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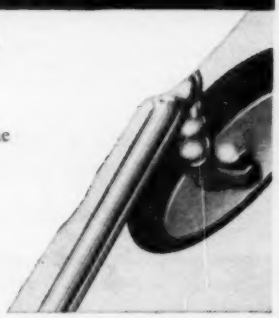

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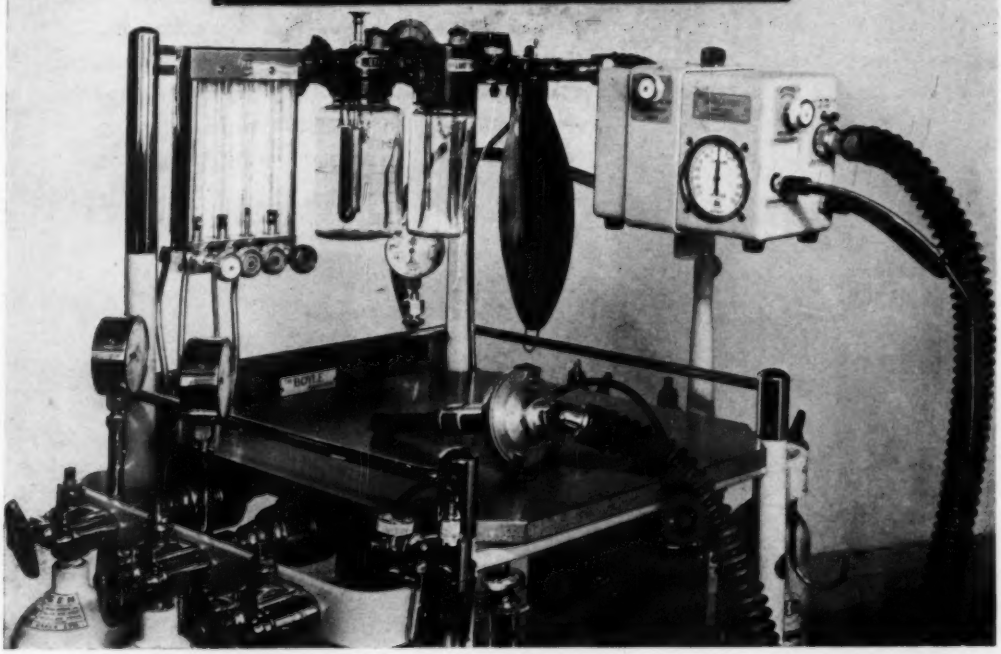

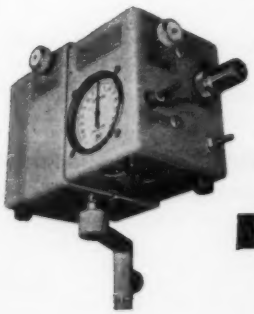

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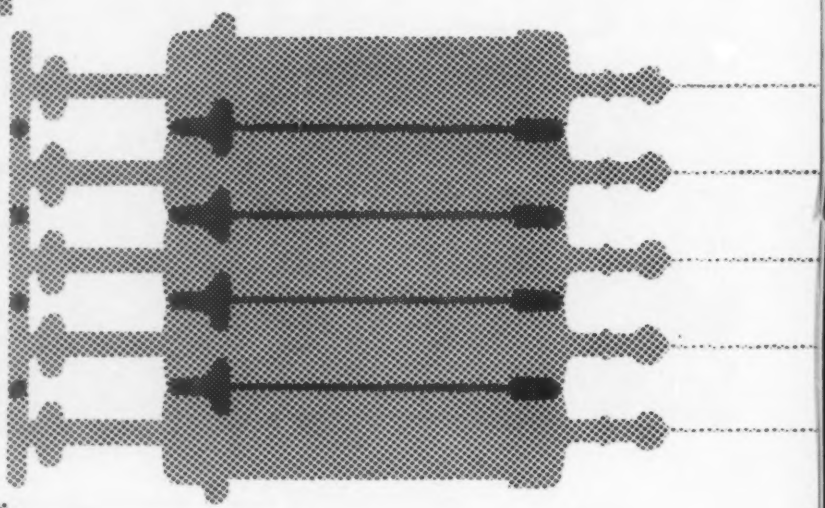

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VOL. XXXIII, No. 5 MAY 1961

EDITORIAL

POUR ENCOURAGER LES AUTRES

THIS journal is written for anaesthetists, mostly by anaesthetists. It therefore serves the useful and indeed essential service of circulating for the benefit of all the experiences and experiments of each. Such is our aim, though in fact we may sometimes fall short of it. There are many reasons for this state of affairs; not the least of these is the reticence of those practising the specialty.

It is well known that the older generation of anaesthetists, perhaps with a few exceptions, was distinguished by that rare and invaluable characteristic of the well-brought-up child, the ability to be seen and not heard. In fact for many years there was no journal especially devoted to anaesthesia in which the anaesthetists of that day could recount their experiences or give expression to their ideas. It is now nearly forty years since the first number of this journal appeared. That disability has therefore been removed, but the diffidence, modesty and shyness still remain and the food on which this journal thrives is supplied by the few.

It is true that many anaesthetists are very busy, but it is generally the busiest men who can find time to do more. R. L. Stevenson suggests that the "practice of letters is miserably harassing to the mind" and threatens that after an hour or two of it a writer may "bully, backbite and speak daggers". For this reason he advises against marrying a writer. We do not believe that those who think of writing for this journal need be deterred by the feeling that there is an ineluctable choice between marital happiness and the writing of an article. The word "relaxant" has a most soothing connotation and should easily overwhelm any tendency to "bully, backbite and speak daggers" that the writing of an article for our journal may have induced in the normally serene mind of the anaesthetist.

Others for one reason or another cannot summon up the energy necessary to make a start. Fear of rejection or criticism may deter some, but it is a poor spirit which is held back by such considerations as these. There certainly should not be any shortage of something to write about. The vast supplies of clinical material in our hospitals which come the way of the registrar anaesthetist do in fact provide the bricks and mortar of many of the papers we publish, but a disproportionate number of such papers come from one or two centres. Stimulus and encouragement seem to have been largely responsible; a wider application of the same would doubtless bring forth good fruit.

Brit. J. Anaesth. (1961), 33, 230

ALTERATIONS IN RESPONSE TO SOMATIC PAIN ASSOCIATED WITH ANAESTHESIA

VI: THE EFFECT ON A NON-BARBITURATE INTRAVENOUS ANAESTHETIC—G.29505

BY

JOHN W. DUNDEE AND R. C. HAMILTON

Department of Anaesthetics, The Queen's University of Belfast, Northern Ireland

ALTHOUGH it has been stated for many years that thiopentone is a poor analgesic, it is only recently that Clutton-Brock (1960) and Dundee (1960a) independently demonstrated that small doses of this drug increase sensitivity to pain. This property appears to be common to all the barbiturates and thiobarbiturates in clinical use, but is not shared by hydroxydione.

Supplies of G.29505, a rapidly acting non-barbiturate intravenous anaesthetic, have been made available to the authors and this paper reports its effect on sensitivity to pain. This compound (2-methoxyl-4-allylphenoxyacetic acid-N, N-diethylamide; *v.* fig. 1) was shown to have narcotic properties by Thuillier and Domenjoz (1957) who with Pulver (1957), Buech (1958), Theobald and Domenjoz (1959) have described some of its pharmacological actions. Most of the clinical reports on the anaesthetic action of G.29505 have been published in Germany (Frey and Herrmann, 1957; Henschel and Just, 1957; Feuerstein, 1957) and these reports have been summarized by Dundee (1960b). They show that the drug produces anaesthesia similar to that which follows the injection of thiopentone, but recovery is much more rapid with the non-barbiturate compound.

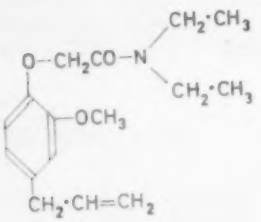

FIG. 1
Formula of G.29505.

METHOD OF STUDY

Sensitivity to pain was measured by the method of analgesimetry described by Dundee and Moore (1960). This consists of the gradual application of measurable degrees of pressure to the anterior surface of the tibia, and two endpoints are employed: (*a*) "threshold"—reading when the sensation of the pressure changes to that of pain; (*b*) "response"—reading when pain is unbearable. For the sake of clarity, the changes in threshold and response readings as compared with the pre-injection controls are reported in preference to absolute readings.

Thirty-six patients of both sexes were observed for this investigation and all received 0.6 mg atropine as pre-anaesthetic medication. The effect of small doses (25–100 mg) was studied prior to the onset of surgery. Observations on the effect of larger doses (200–1000 mg) were carried out during recovery from anaesthesia for uterine curettage, during which G.29505 was the sole anaesthetic agent.

RESULTS

With 25-mg doses of G.29505, consciousness was not lost and there was usually a slight increase in both the pain threshold and response readings, lasting from ½ to 3 minutes. An increased sensitivity to pain was not observed in any patient.

Doses of 50 mg frequently, but not invariably, resulted in a brief period of unconsciousness and this was accompanied by a marked rise in response readings (as judged by readings when the leg was moved in response to the stimulus). The onset of sleep occurred about 20 seconds after injection and patients usually opened their eyes about 1½ to 2 minutes later. However, decreased sensitivity to

pain persisted for about 1 further minute (fig. 2).

The average effects of 25, 50 and 100-mg doses are shown in figure 3 and demonstrate the analgesic action of small doses of G.29505. With both these and larger doses, it was often noted that the pain threshold readings returned to within the normal range before the response readings, although this difference is not very evident in figure 3 because of the brief times involved.

whereas with large doses of 8 to 18 mg/kg this effect has been detected for up to 1 hour after administration, which is about 50 minutes after the return of consciousness.

In the total series of 36 patients on whom 169 observations were carried out following doses of G.29505 ranging from 25 to 1000 mg, a significant increase in sensitivity to pain was only detected on four occasions, and in each instance the subsequent

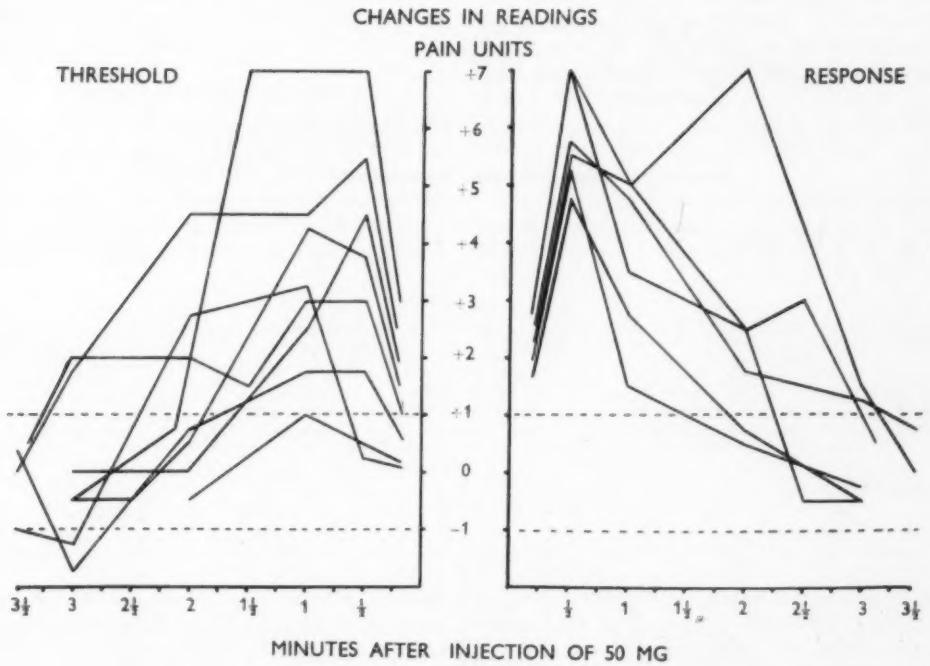

FIG. 2
The effect of 50 mg of G.29505 on pain threshold and response readings.

The administration of doses in excess of 100 mg was spread over a period of 2 to 10 minutes and readings are timed from the midpoint of the administration. In presenting the findings, it has proved convenient to consider the sum of threshold and response readings and to divide the data into that for 200–300 mg and for 375–1000-mg doses (fig. 4). This figure shows that the analgesic action of moderate doses (4–7 mg/kg) of G.29505 lasts for about 30 minutes after injection of the drug,

reading was within the range of the initial control reading. In one patient, this occurred 120 minutes after dose of 11 mg/kg, but the next reading at 135 minutes was slightly above the initial control (the time scale in figure 4 does not permit these readings to be shown). Two patients showed a decrease in response readings within the first minute after the administration of 25 mg of the drug and it was difficult to be sure that they were able to distinguish between the two endpoints. The fourth

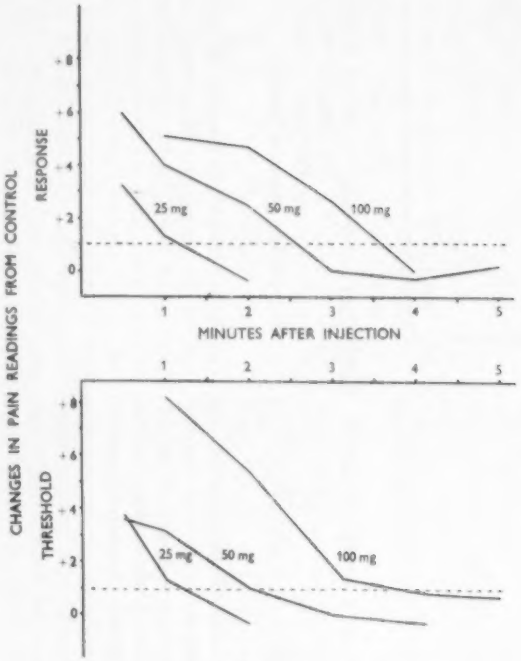

FIG. 3

Comparison of the analgesic effects of 25, 50 and 100 mg doses of G.29505 on pain threshold and response readings.

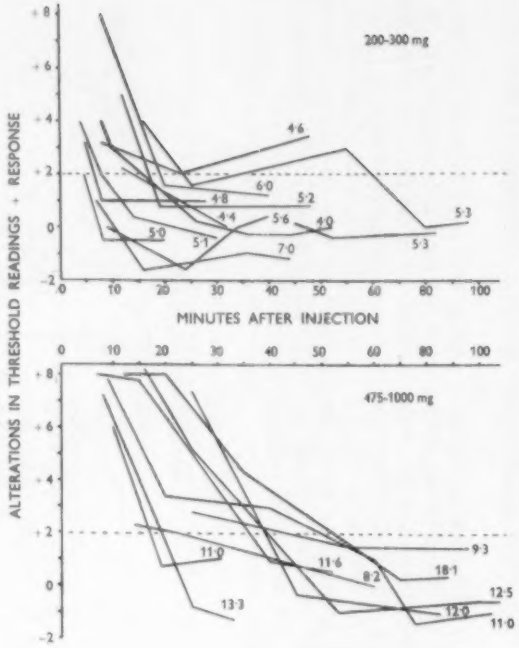

FIG. 4

The effect of large doses of G.29505 on pain threshold and response readings.

instance occurred 24 minutes after the injection of 175 mg and coincided with severe colicky abdominal pain.

One feature of this investigation, as compared with similar studies with the barbiturates, was the co-operation of the patients, even in the period immediately after recovery. Only one result had to be discarded for this reason, whereas about one-fifth of patients who had received thiopentone (and a much higher percentage after pentobarbitone) were either unable or refused to co-operate until an appreciable time after recovery.

COMPARISON WITH OTHER DRUGS

These findings are directly opposite to those observed with thiopentone, but they also differ in the time taken for pain readings to return to normal control values. One can never be sure of this time, but an approximate comparison between the duration of action of the two drugs is shown in table I.

DISCUSSION

From these findings one would expect G.29505 to be eminently suitable for use as a sole anaesthetic for minor operations. This is borne out fully by the authors' experiences with the drug and by the reports of Henschel and Just (1957) and Boureau (1960), although Frey and Herrmann (1957) and Feuerstein (1957) recommend that it be combined with nitrous oxide and oxygen. About half a minute after the injection of 3 to 5 mg/kg of G.29505, incision of abscesses, manipulation of fractures or reduction of dislocations can be carried out easily, although the brevity of action limits the operating time to 1 to 2 minutes.

Suturing or dressing is usually possible even though the patient may have recovered to the extent of opening his eyes.

There is no evidence to show whether the brief period of analgesia which follows recovery from large doses is of any significance in the post-operative period. The clinical experience of the writers with large doses is very limited, but despite the invariable immediate complete return of consciousness an analgesic has never had to be administered before the patient returned to the ward.

Animal experiments, reported by Thuiller and Domenjoz (1957), have demonstrated an analgesic action following the oral administration of G.29505, although Rapp (1957) found that it possessed no analgesic properties when tested by the Hardy-Wolff method. Rapp's dosage was 3 mg/kg and his failure to detect analgesia may well be due to the brevity of action of small doses of G.29505 as shown in figures 2 and 3. The time required for application of the radiant heat method of analgesimetry is such that the rapidly waning

TABLE I

Average times for return to normal threshold and response readings following G.29505 and thiopentone.

Range of dosage (mg)	G.29505		Thiopentone	
	Average dose (mg/kg)	Average time for readings to return to normal (min)	Average dose (mg/kg)	Average time for readings to return to normal (min)
50	—	2.5	—	2.5
100–200	2.3	4.5	2.1	6.0
250–500	5.4	21	5.0	68
500+	9.5	35	8.1	105

Data for thiopentone is taken from a previous study carried out by one of the authors (Dundee, 1960a). The cases for comparison had to be carefully chosen as being those in whom a series of readings were made over a short period of time and gave values close to those observed before injection of the drug. It can be seen that the brevity of the analgesic action of G.29505, as compared with that of the anti-analgesic action of thiopentone is most marked when large doses are employed.

Hydroxydione and G.29505 are so dissimilar in their anaesthetic effects that it is not possible to make a direct comparison of their actions on pain threshold and response readings. Both decrease sensitivity to pain, but the time of onset and duration of effect is much shorter with G.29505 than with the steroid.

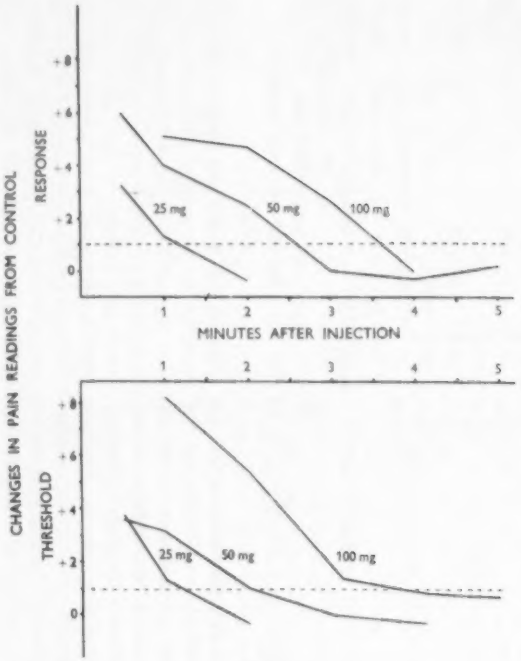

FIG. 3

Comparison of the analgesic effects of 25, 50 and 100 mg doses of G.29505 on pain threshold and response readings.

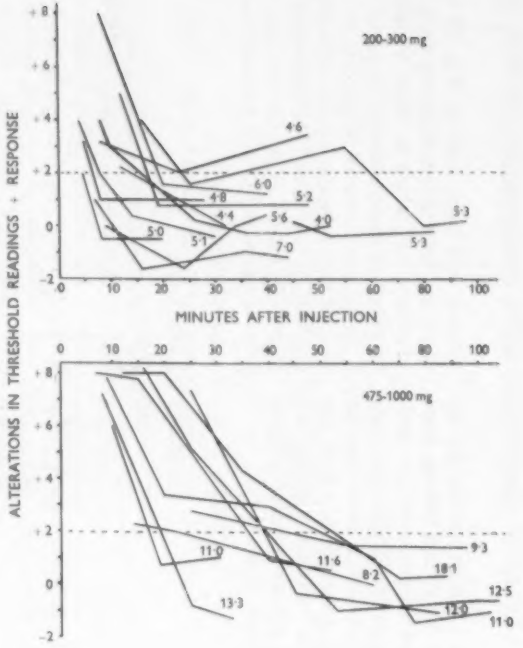

FIG. 4

The effect of large doses of G.29505 on pain threshold and response readings.

instance occurred 24 minutes after the injection of 175 mg and coincided with severe colicky abdominal pain.

One feature of this investigation, as compared with similar studies with the barbiturates, was the co-operation of the patients, even in the period immediately after recovery. Only one result had to be discarded for this reason, whereas about one-fifth of patients who had received thiopentone (and a much higher percentage after pentobarbitone) were either unable or refused to co-operate until an appreciable time after recovery.

COMPARISON WITH OTHER DRUGS

These findings are directly opposite to those observed with thiopentone, but they also differ in the time taken for pain readings to return to normal control values. One can never be sure of this time, but an approximate comparison between the duration of action of the two drugs is shown in table I.

TABLE I

Average times for return to normal threshold and response readings following G.29505 and thiopentone.

	G.29505		Thiopentone	
Range of dosage (mg)	Average dose (mg/kg)	Average time for readings to return to normal (min)	Average dose (mg/kg)	Average time for readings to return to normal (min)
50	—	2.5	—	2.5
100–200	2.3	4.5	2.1	6.0
250–500	5.4	21	5.0	68
500+	9.5	35	8.1	105

Data for thiopentone is taken from a previous study carried out by one of the authors (Dundee, 1960a). The cases for comparison had to be carefully chosen as being those in whom a series of readings were made over a short period of time and gave values close to those observed before injection of the drug. It can be seen that the brevity of the analgesic action of G.29505, as compared with that of the anti-analgesic action of thiopentone is most marked when large doses are employed.

Hydroxydione and G.29505 are so dissimilar in their anaesthetic effects that it is not possible to make a direct comparison of their actions on pain threshold and response readings. Both decrease sensitivity to pain, but the time of onset and duration of effect is much shorter with G.29505 than with the steroid.

DISCUSSION

From these findings one would expect G.29505 to be eminently suitable for use as a sole anaesthetic for minor operations. This is borne out fully by the authors' experiences with the drug and by the reports of Henschel and Just (1957) and Boureau (1960), although Frey and Herrmann (1957) and Feuerstein (1957) recommend that it be combined with nitrous oxide and oxygen. About half a minute after the injection of 3 to 5 mg/kg of G.29505, incision of abscesses, manipulation of fractures or reduction of dislocations can be carried out easily, although the brevity of action limits the operating time to 1 to 2 minutes.

Suturing or dressing is usually possible even though the patient may have recovered to the extent of opening his eyes.

There is no evidence to show whether the brief period of analgesia which follows recovery from large doses is of any significance in the post-operative period. The clinical experience of the writers with large doses is very limited, but despite the invariable immediate complete return of consciousness an analgesic has never had to be administered before the patient returned to the ward.

Animal experiments, reported by Thuiller and Domenjoz (1957), have demonstrated an analgesic action following the oral administration of G.29505, although Rapp (1957) found that it possessed no analgesic properties when tested by the Hardy-Wolff method. Rapp's dosage was 3 mg/kg and his failure to detect analgesia may well be due to the brevity of action of small doses of G.29505 as shown in figures 2 and 3. The time required for application of the radiant heat method of analgesimetry is such that the rapidly waning

analgesia following the injection of the drug may be missed.

G.29505 is a compound unrelated to any other drug used in anaesthesia. Its introduction and the demonstration of its analgesic action opens up a new field in the search for the ideal intravenous anaesthetic. This drug itself may eventually prove not to be the final answer, but its properties suggest that the phenoxyacetic acid amines are compounds to which the research chemists and pharmacologists might, with benefit, direct their attention.

SUMMARY

Analgesimetry studies have been carried out on a new non-barbiturate intravenous anaesthetic—G.29505 (2-methoxyl-4-allylphenoxyacetic acid-N, N-diethylamide). The method employed consisted of the application of graded pressure to the anterior surface of the tibia. In contradistinction to the action of thiopentone, subhypnotic doses of G.29505 decrease the sensitivity to somatic pain. This effect was very transient. During the recovery period after larger doses of the drug, there was a gradual return of readings to normal but at no time was an anti-analgesic action detected. Even with large doses, the duration of this analgesic effect was very short.

The clinical significance of these findings has been discussed and in this, or related compounds, an intravenous anaesthetic may be found which can be used safely for short procedures without supplementary nitrous oxide and oxygen.

ACKNOWLEDGMENTS

Generous supplies of G.29505 were provided by Dr. J. P. Birkett of Geigy Ltd., to whom we are indebted for his help in various facets of this study. Thanks are also due to Mr. O. J. Smith for preparation of the illustrations.

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A DEVICE FOR ESTIMATING THE MINUTE VOLUME DELIVERED BY AN IPP RESPIRATOR

BY

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IT is not easy to make accurate measurements of the minute volume delivered by an IPP respirator Cooper, 1959). Even the electronic integrating pneumotachygraph (Pressey, 1952) has the disadvantages of bulk, fire risk, complexity, and the likelihood of error arising from zero drift. Further, its calibration factor is a function of the physical properties of the gases passing. In anaesthesia these may be neither constant nor precisely known.

DESCRIPTION OF THE NEW DEVICE

Principle.

Figure 1 represents a tube (about 3 cm in diameter) with a fine gauze stretched across it.

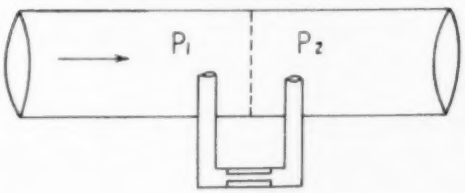

FIG. 1

The principle of the device. When gas flows in the direction of the arrow there is a difference between the pressures P1 and P2 owing to the resistance of the gauze diaphragm.

The gauze is bypassed by a smaller tube (about 2 mm in diameter) which contains an additional constriction (a 2 cm length of tube having an internal diameter of 0.6 mm). When gas is flowing in the tube the pressure P1 is greater than the pressure P2. The difference causes some gas to flow through the bypass. The pressure difference (P1 – P2) is not necessarily proportional to the rates of flow through either channel but it has been found possible, by trial and error, to match the characteristics of the gauze and the constriction so that the relationship between the two rates of flow is definable and reasonably constant. Since the same gas mixture flows through both systems, small changes in its viscosity are not of major importance and only approximate knowledge of its composition is necessary for accurate calibration. The arrangement may be regarded as a pneumatic version of the "shunting" of current through a low resistance in parallel with a sensitive electrical meter. The measurement of the small gas flow through the bypass is made from the movement of a soap film formed across it (Barr, 1934).

The practical device.

Figure 2 shows a scale drawing of the two parts of the device. It will not be described in greater detail since the few dimensions which are critical were determined by trial and error and are given in the text. Figure 2A shows the valve unit which, apart from the flaps of the valves, is made of brass. The gauze resistance is of double thickness, mounted after a filter made of the same gauze (350 mesh) to prevent occlusion of the pores by dust, and hence alteration of calibration. The rates of flow in the main and bypass channels are in the approximate ratio of 600:1. A small pressure-equalizing channel passes from the inspiratory to expiratory tubes since otherwise, when using an IPP respirator producing a square wave, the calibration factor of the meter varies with the respiratory frequency. Figures 2B and 2C show the measuring unit which is made of Perspex. It is connected to the valve unit by two rubber tubes, 90 cm long. The soap film passes down the inclined tube which is graduated in centimetres. The tap at the bottom of the slope

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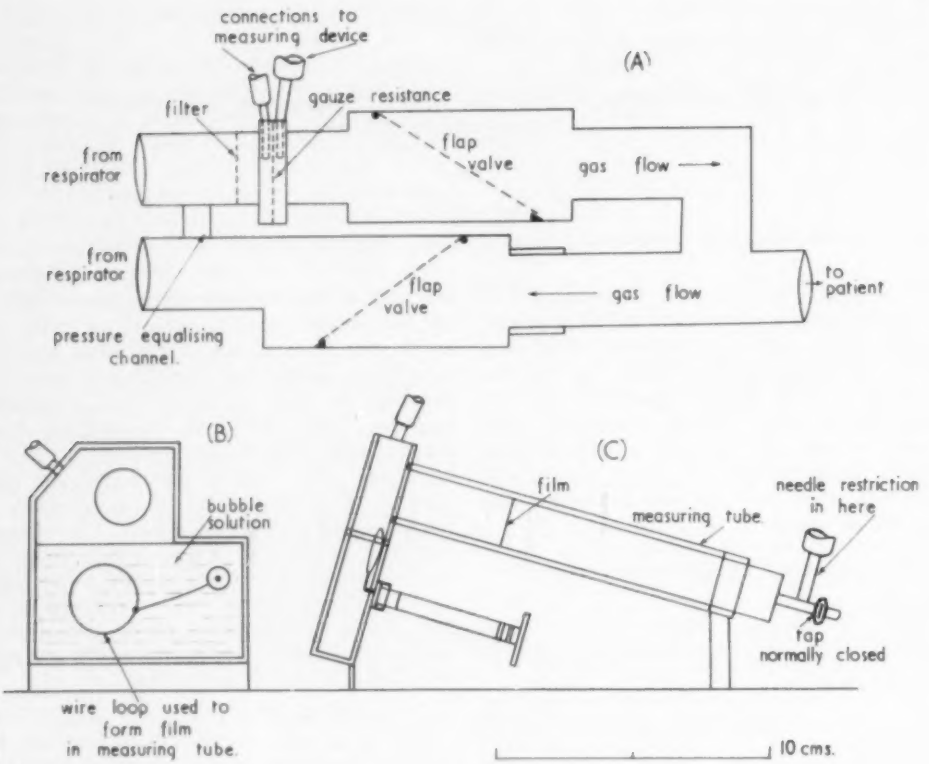

FIG. 2

Diagram of the device.
(A) Valve unit.
(B) Measuring unit, as seen end on.
(C) Measuring unit, side view.

is to allow drainage of soap solution and flushing of the apparatus if the composition of the gases is changed abruptly.

VALIDATION OF THE DEVICE BY EXPERIMENT

The only experiments reported here are those in which a mock patient was ventilated by an IPP respirator. The minute volume was estimated by the new device and simultaneous measurements were made by a second experimental system of known high accuracy. The respirator has been described elsewhere (type 1 of Horton, Inkster and Pask, 1956). Since its mechanism abruptly intermits the flow of fresh gases from a constant pressure reservoir to the patient it is of the "square wave" type. The elastic properties of the mock patient were provided by a bellows having compliance 43 ml/cm H_2O for the first 10 cm increase in pressure and 34 ml/cm for a pressure change of 20 cm H_2O. This compared well with the suggested average compliance of 40 ml/cm for patients receiving artificial respiration (Elam, Kerr and Janney, 1958). The frictional resistance of the mock patient was satisfactorily close to the suggested value of 2 cm H_2O/l./sec of Zechman, Hall and Hull (1957).

The first experiments were carried out with air. The bellows of the mock patient were enclosed in a rigid Perspex box. The volume of air dis-

placed per minute by the inflation of the bellows was measured by a dry gas meter (error ±30 ml in 10 l.) in a valved system of negligible slip. Appropriate corrections were made for the compressibility of the air in the system (in the range 7 to 40 ml/cycle). The calibration factor of the device was expressed as cm travel of the soap film per litre of air passed. The effects of changes in the following variables were investigated.

Compliance. No alteration of calibration factor was observed when the compliance of the mock patient was halved.

Frictional resistance. When the peak pressure in the system was kept constant there was no significant variation of calibration factor with frictional resistance in the range 0–16 cm H_2O/l./sec. For instance, with the standard mock patient the mean of ten values was 0.656 (range 0.646–0.673). With the resistance removed the mean of ten results was 0.658 (0.651–0.672).

Frequency. Provided that peak pressure was not altered the calibration factor was independent of the frequency of cycling up to 40 c.p.m. This is shown in table I.

TABLE I

The relationship between the calibration factor and the respiratory frequency.

Frequency c.p.m.	Calibration factor cm/l.
7	0.68
9	0.68
17	0.69
19	0.69
31	0.69
33	0.68
41	0.69
44	0.68
48	0.66
64	0.67
65	0.65

Minute volume. The above results implied that when the peak pressure was constant the calibration factor would not vary with minute volume. Confirmation of this is shown in table II.

Composition of gases. The calibration factor for nitrous oxide was 8 per cent lower than that for oxygen and the variation was in direct proportion to the percentage of nitrous oxide in the mixture. Thus a 10 per cent variation in composition resulted in less than 1 per cent change in the calibration factor.

TABLE II

The constancy of the calibration factor at various minute volumes

Minute volume l./min	Variation of calibration factor from mean (%)
5.27	−0.64
6.13	+0.64
6.91	−0.64
8.08	+0.32
8.63	−0.32
10.4	+0.32
12.4	+0.32
12.5	+1.12
12.9	−0.48
12.9	−1.12

Peak pressure applied to the mock patient. A final extensive series of experiments was carried out in which the standard mock patient was ventilated with a mixture of 70 per cent nitrous oxide in oxygen. Variations in the peak pressure caused variations in the calibration but alteration of other variables within the relevant physiological range had no systematic effect. Figure 3 shows the results of fifty determinations of the calibration factor. The range of pressure was 8–32 cm H_2O; of frequencies 6–20 c.p.m.; of tidal volumes 280–800 ml; of minute volumes 2–9 l./min. The solid line was fitted by eye. It represents a calibration factor of 0.625 at a peak pressure of 14 cm H_2O, increasing by 0.002 per cm H_2O increase in pressure. The standard deviation of the fifty points about the line was ±0.0154 or 2.46 per cent. The broken lines represent mean ± S.D. Owing to the experimental method used, this variation in calibration factor with pressure includes the correction for the compressibility of the gases in the system between the resistance gauze and the mock patient.

Justification for the use of the device rests upon the measured volume being truly fresh gas, not significantly contaminated by previous expirate. Extensive tests of the slip of the valves established that the quantity of expired gases reintroduced was unlikely to exceed 2 ml/cycle, which could be ignored.

It is also important for the validity of physiological measurements that the resistance to the patient's expiration is small. The resistance of the device was largely independent of the rate of flow in the relevant range. The opening pressure of the valve was 0.5 cm H_2O, which was

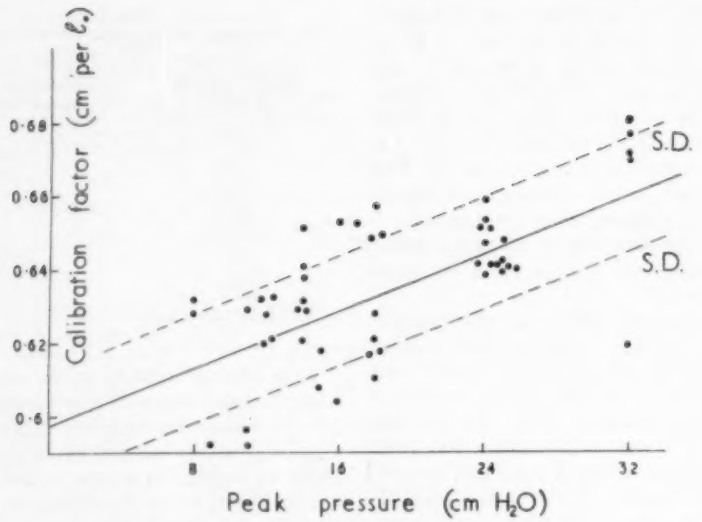

FIG. 3
The relationship between the calibration factor and the peak pressure applied to the mock patient.

also the pressure required to maintain a constant flow of 1 l./sec. through the expiratory path.

SUMMARY

A simple pneumatic device is described for measuring the minute volume of patients on IPP respirators.

ACKNOWLEDGMENT

We are very grateful to Professor E. A. Pask for his help and suggestions during the development of this instrument.

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CHLOROFORM AND HALOTHANE IN A PRECISION SYSTEM

*Comparison of Some Cardiovascular, Respiratory and Metabolic Effects in Dogs**

BY

ALLEN B. DOBKIN,† JOHN H. HARLAND‡ AND SYLVIA FEDORUK

THIS study was undertaken to compare certain important effects of chloroform and halothane, under conditions closely simulating their modern clinical use. These two agents have many properties in common. They naturally invite comparison and both have their ardent advocates. The chloroform controversy still rages in the medical press and cannot fail to interest the practising anaesthetist. While not ourselves holding any partisan views on the relative merits of these two agents, both of which we have used successfully both clinically and in the laboratory, we tend to hold the view that they are not the only available potent anaesthetics, and that comparison of their relative merits is of interest mostly to the academic anaesthetist, and further, that neither one has a very substantial advantage over the other.

The argument in its simplest form may be stated thus. The upholders of chloroform point to the price difference and argue that on a cost basis alone halothane would have to transcend chloroform in safety and general usefulness before one could justify its use. The proponents of halothane, on the other hand, urge that however valid this argument may be in the under-developed areas of the world, in our consumer-oriented society, cost should not be considered, especially in such an important step as anaesthetizing a human being for surgery. They argue, and with some reservations we feel with justice, that some manufacturer can always produce a second-rate cheap substitute for any first-class article, and in John Ruskin's elegant, if cynical, phrase, "Nobody has ever made anything which someone else cannot make less well and more cheaply. Those who consider price alone are this man's lawful prey."

This study did produce some findings of interest, which may ultimately help to settle the place of these two agents in the scheme of things. In particular it drew to our attention the fact that there are definite species differences in their actions and we were again made cognizant of the dangers of a too enthusiastic and uncritical application of laboratory findings to the conditions that obtain in the operating room. It also reminded us that the first members of every group of drugs which have been used for a long time, may still be considered efficacious (Waters, 1951; Dittrick, 1951; Armstrong Davison, 1959; Bamforth, et al., 1960; Dobkin, Skinner and Johnston, 1960; Poe and Mayfield, 1960).

MATERIALS AND METHODS

After preliminary experimental trials, chloroform and halothane anaesthetics were administered to twenty-nine mongrel dogs weighing 13.2 kg to 20.9 kg (mean 17.3 kg).

Table I summarizes the experiments done. Twenty dogs received both anaesthetics consecutively on two separate occasions (experiments 2A, 4B, 4C, 10E). Five dogs received each anaesthetic once on two separate occasions (experiment 5D). Four dogs died at various stages of the experiments (1B, 1C, and 2E).

Alternate animals were given halothane or chloroform first in order to eliminate the possibility of a significant effect due solely to the order of administration of the anaesthetics. In the seventeen dogs which were not permitted to breathe spontaneously (experiments 5D, 12E), pulmonary ventilation was augmented with a Takaoka respirator.

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TABLE I

Summary of experiments comparing halothane and chloroform in dogs.

No. of dogs	Anaesthetic	Inhaled concentration	Duration (minutes)	Breathing	Remarks
2A	Halothane	2%	60	Spontaneous	
2A	Chloroform	1.5%	60	Spontaneous	
2A	Chloroform	1.5%	60	Spontaneous	
2A	Halothane	2%	60	Spontaneous	
5B	Chloroform	1.5%	90	Spontaneous	
5B	Halothane	2%	90	Spontaneous	
5B	Halothane	2%	90	Spontaneous	One dog died
4B	Chloroform	1.5%	90	Spontaneous	during experiment
4C	Halothane	2%	120	Spontaneous	
4C	Chloroform	2%	120	Spontaneous	
5C	Chloroform	2%	120	Spontaneous	One dog died
4C	Halothane	2%	120	Spontaneous	during experiment
5D	Chloroform	1%	120	Augmented	
5D	Halothane	2%	120	Augmented	
12E	Halothane	2%	90	Augmented	Two dogs died
12E	Chloroform	0.8%	90	Augmented	several days after
10E	Chloroform	0.8%	90	Augmented	experiment
10E	Halothane	2%	90	Augmented	

When the two agents were given consecutively, oxygen was administered between the anaesthetics until the animal reacted on the endotracheal tube; other than this, no attempt was made to eliminate completely the previous agent before the study was resumed with the second anaesthetic. Six weeks later, the experiments were repeated and the order of administering the anaesthetics was reversed.

One hour before each experiment, the dogs were premedicated with 5 mg perphenazine and 0.4 mg atropine intramuscularly. Light anaesthesia was then induced with a "sleep" dose of thiopentone (75 to 150 mg) and an endotracheal tube was placed in the trachea.

The halothane and chloroform were vaporized with oxygen using a calibrated Fluotec and Chlorotec respectively. No rebreathing occurred. In the experiments where spontaneous breathing was permitted, a non-return valve was employed, while in those animals in which breathing was augmented with a Takaoka respirator, the expired gases escaped automatically into the atmosphere.

Whenever any of the dogs who were allowed to breathe spontaneously became apnoeic, the anaesthetic was turned off and ventilation was maintained by manual compression of an oxygen reservoir bag until respiratory efforts returned. Then anaesthesia was resumed.

The concentrations of the agents used in this study were chosen on the basis of their ability to maintain a light but steady plane of surgical anaesthesia in dogs. It was recognized that the animals whose breathing was augmented would have a higher alveolar and blood tension of the anaesthetic vapour than would those breathing spontaneously. However, no attempt was made to regulate anything other than the inhaled concentration. In the preliminary experiments it was found that severe circulatory depression occurred when the concentration of halothane exceeded 2 per cent. Lesser concentrations of halothane anaesthesia were insufficient to maintain unconsciousness. Therefore 2 per cent halothane was used during all of the experiments. It was found that a lower vapour concentration of chloroform (0.8 to 1 per cent) maintained adequate anaesthesia when breathing was augmented than that required when breathing was spontaneous (1.5 to 2 per cent). Accordingly, a lower concentration

TABLE II

Summary of some metabolic effects of 2% halothane and 1.5% chloroform in 2 dogs breathing spontaneously for 60 minutes.

	Control	2% Halothane 60 minutes	1.5% Chloroform 60 minutes	Control	1.5% Chloroform 60 minutes	2% Halothane 60 minutes
pH	7.33	7.26	7.23	7.36	7.17	7.22
Total CO_2 mM/L	23.5	24	23.5	23	24	22.5
Pco_2 mm Hg	44	53	54	40	65	53
HCO_3—mM/L	22	22.5	22	22	22	21
O_2 saturation %	89	89	97	80	84	100
Hematocrit	37	39	38	36	40	35
Potassium m.equiv/l.	3.3	3.8	3.7	3.7	4.0	4.0
Sodium m.equiv/l.	161	167	175	158	168	161
Chloride m.equiv/l.	113	112	115	121	117	120
Glucose mg%	93	78	90	84	200	95
CCF* Control	0	0	0	0	0	0
24 hour	1.5	1	3	2	1	2.5
48 hour	1.5	1	2	1.5	1	2.5

*Cephalin cholesterol flocculation.

TABLE III

Summary of some metabolic effects of 2% halothane and 1.5% chloroform in 4 dogs breathing spontaneously for 90 minutes.

	Control	2% Halothane 90 minutes	1.5% Chloroform 90 minutes	Control	1.5% Chloroform 90 minutes	2% Halothane 90 minutes
pH	7.30	7.19	7.06	7.34	7.19	7.04
Total CO_2 mM/l.	21.5	23	24	22	21	24
Pco_2 mm Hg	43	59	91	40	59	88
HCO_3—mM/l.	20	21	21.5	21	19	21.5
O_2 saturation %	89	98	93	91	93	98
Hematocrit	36	34	46	36	39	37
Potassium m.equiv/l.	3.7	4.0	3.6	3.4	3.3	4.2
Sodium m.equiv/l.	161	165	167	166	170	166
Chloride m.equiv/l.	115	115	116	116	114	116
Glucose mg%	91	89	154	84	142	153
CCF* Control	0	0	0	0	0	0
24 hour	2	1.5	1.5	1.5	1	1.5
48 hour	2	1.5	1.5	1.5	1	1

*Cephalin cholesterol flocculation

TABLE IV

Summary of some metabolic effects of 2% halothane and 2% chloroform in 4 dogs breathing spontaneously for 120 minutes.

	Control	2% Halothane 120 minutes	2% Chloroform 120 minutes	Control	2% Chloroform 120 minutes	2% Halothane 120 minutes
pH	7.35	7.16	7.15	7.22	7.05	7.10
Total CO_2 mM/l.	21.5	24.5	23.5	22	24	23
Pco_2 mm Hg	38	66	66	52	65	70
HCO_3—mM/l.	20.5	22.5	21.5	20.5	22	21
O_2 saturation %	82	96	92	89	89	92
Hematocrit	35	32	39	31	39	33
Potassium m.equiv/l.	3.6	3.7	3.8	3.4	3.9	4.7
Sodium m.equiv/l.	172	164	165	164	164	167
Chloride m.equiv/l.	115	115	116	112	113	114
Glucose mg%	92	90	131	90	169	151
CCF* Control	0	0	0	0	0	0
24 hour	2	1.5	1.5	1.5	1	1
48 hour	2	1.5	1.5	1.5	1	1.5

*Cephalin cholesterol flocculation.

TABLE V

Summary of some metabolic effects of 2% halothane and 0·8% chloroform in dogs with augmented breathing for 90 minutes.

	Control*	2% Halothane 90 minutes	0·8% Chloroform 90 minutes	Control†	0.8% Chloroform 90 minutes	2% Halothane 90 minutes
pH	7.30	7.19	7.22	7.27	7.12	7.12
S.D.	0.06	0.13	0.13	0.05	0.13	0.09
Total CO_2 mM/l.	23	24.5	24	22	22	23.5
S.D.	1.4	2.4	1.8	1.1	2.5	2.5
Pco_2 mm Hg	46	64	58	48	67	71
S.D.	5.8	21.5	17	5.6	23.5	18
HCO_3—mM/l.	21.5	22.5	22.5	20.5	20	21.5
O_2% saturation	85	98	96	82	95	96
S.D.	5	3.6	4.5	8.5	7.3	4.6
Hematocrit	42	40	42	41	41	40
S.D.	3.5	3.2	3.9	3.5	4.3	4.2
Sodium m.equiv/l.	154	156	153	155	158	154
S.D.	6.7	7.2	6.6	5.8	7.3	7.3
Potassium m.equiv/l.	3.7	3.9	3.6	3.8	3.8	4.0
S.D.	.15	.45	.23	.25	.50	.74
Chloride m.equiv./l.	118	118	119	121	121	123
S.D.	4.9	5.3	5.1	3.5	5.3	4.7
Glucose mg%	87	88	92	87	105	109
S.D.	11	10.7	28	10	44	44
CCF‡ Control	0	0	0	0	0	0
24 hour	2.5	2.5	2	2.5	2.5	2
48 hour	2	2	2	2	1.5	1.5

*12 dogs. †10 dogs. ‡Cephalin cholesterol flocculation.

of chloroform was used in the experiments where breathing was augmented.

The anaesthetic agents were not administered initially until the monitoring equipment had been set up, initial readings made and blood samples withdrawn for "control" determinations. Sufficient time elapsed between the thiopentone injected at the beginning and the experiment proper to be certain that this drug would not affect significantly the physiological and chemical variables being measured. At the end of each experiment the administration of oxygen was continued until the animal reacted to the endotracheal tube.

Anaerobic arterial blood and venous blood samples were withdrawn at the start of each experiment and when the administration of each of the two anaesthetics was discontinued. These were analyzed by standard laboratory techniques to determine the arterial pH (Beckman GS pH meter, Wilson, 1951), total CO_2 (modified van Slyke manometric method, van Slyke and Neill, 1924; Singer and Hastings, 1948), oxygen saturation (D U spectrophotometer, Nahas, 1950; Hickman and Frayser, 1952), haematocrit (Natelson method, 1951), plasma chloride (method of Schales and Schales, 1941), plasma sodium and potassium (method with flame photometer), blood glucose (Folin and Wu method, 1919) and cephalin cholesterol flocculation (Hanger method, 1939).

Arterial and venous blood pressures were recorded with cannulae inserted through the femoral artery into the aorta and through the femoral vein into the inferior vena cava. Both were attached to Statham strain gauges. The cannulae were flushed as required with small amounts of heparinized saline. No glucose was administered in any of the experiments. A Wright respirometer was interposed between the endotracheal tube and the non-return valve or the Takaoka respirator in order to record the minute volume of breathing. Rate of respiration was measured with a belt-type pneumotachograph. Lead 2 of the electrocardiogram, blood pressures (arterial and venous) and the pneumotachograph tracings were recorded continuously throughout the periods of anaesthesia on a Grass polygraph ink recorder. The record paper speed was set at 18 cm/min except at 10-minute intervals, when it was allowed to run briefly at 180 cm/min, in order to facilitate analysis of the tracings at these intervals.

Serial cardiac output estimations were made by a technique previously reported, using radioactive iodinated human serum albumin injections (Dobkin, Harland and Fedoruk, 1960). This method has been found to be reliable (Huff et al., 1955; Thompson et al., 1959).

The data derived from the tracings in each experiment were tabulated and graphed in order to show the mean values at 10-minute intervals. This was obtained from the individual mean values over a representative 10-second strip of the recording. Blood chemistry data and cardiac output estimations were analyzed at three points (control and at the end of each anaesthetic). In the five dogs receiving each agent once only, cardiac output was measured at 30-minute intervals.

RESULTS

Anion-cation balance. Progressive respiratory acidosis occurred in all experiments in which the dogs were permitted to breathe spontaneously. Chloroform tended to cause in addition a slight metabolic acidosis when anaesthesia exceeded 60 minutes. Metabolic acidosis did not occur when halothane was used. When respiration was augmented, the change toward anion-cation imbalance was much reduced. Apart from the tendency of chloroform to cause metabolic acidosis, there was no appreciable difference in the response to the two agents (figs. 1 to 9).

Serum electrolytes. There was a rise in serum potassium during the administration of halothane in every experiment, both when breathing was spontaneous and when it was augmented. Chloroform, however, had this effect to a much lesser degree when breathing was spontaneous, and when breathing was augmented the effect disappeared completely. No alteration in serum sodium or serum chloride occurred in any of the experiments (tables II, III, IV, V).

Blood glucose and cephalin cholesterol flocculation. Chloroform caused a rise in the blood glucose in some of the dogs when breathing was spontaneous. This effect was almost eliminated when breathing was augmented. Halothane did not cause a rise in the blood glucose, indeed after most of the experiments, the blood glucose was slightly lower.

Cephalin cholesterol flocculation was raised

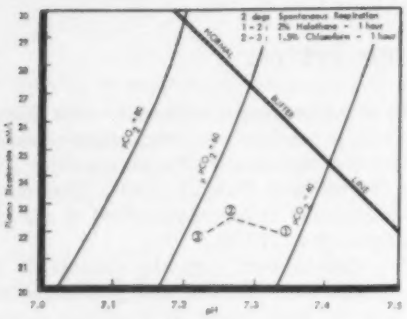

FIG. 1

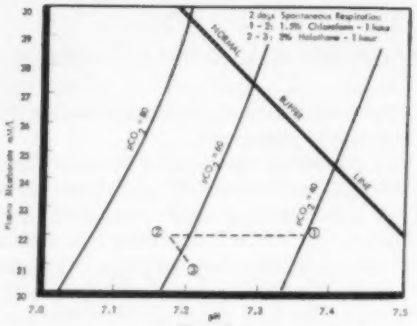

FIG. 2

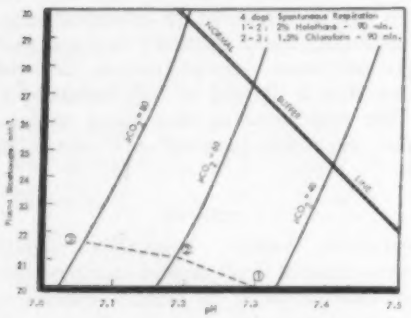

FIG. 3

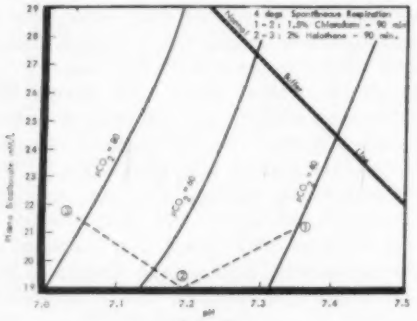

FIG. 4

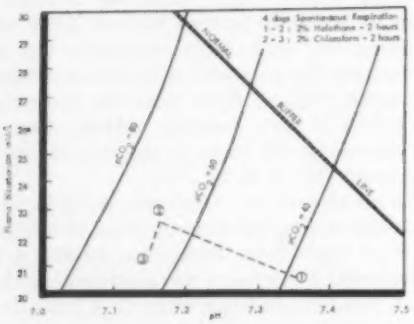

FIG. 5

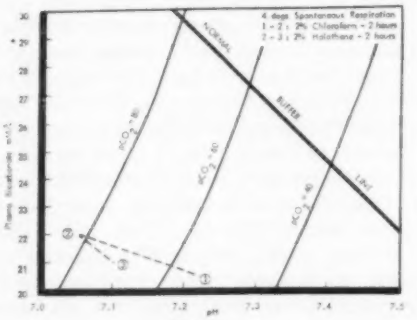

FIG. 6

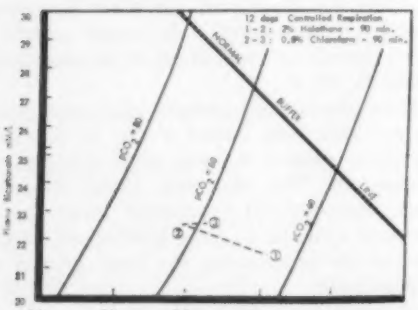

FIG. 7

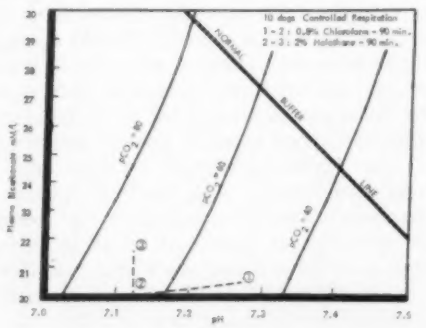

FIG. 8

FIGS. 1 TO 8
Anion-cation balance before and at the end of anaesthetic periods of chloroform and halothane.

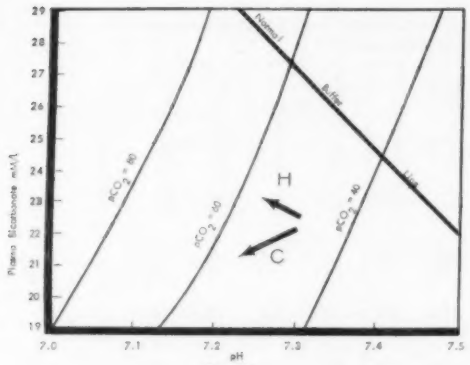

FIG. 9

Anion-cation balance: effect of 2 per cent halothane and 1 per cent chloroform for 120 minutes each on separate occasions (5 dogs, breathing augmented).

slightly during the administration of both anaesthetic agents. The effect was the same with halothane and chloroform whether breathing was spontaneous or augmented (tables II to V).

Haematocrit and oxygen saturation. During spontaneous breathing there was a tendency for the haematocrit to increase during chloroform anaesthesia. This effect was absent when breathing was augmented. On the other hand, there was a tendency toward lowering of the haematocrit during halothane anaesthesia. These changes were very slight. During every experiment the oxygen saturation of the arterial blood rose, regardless of which anaesthetic was being administered (tables II to VI).

TABLE VI

Effect of 2% halothane and 1% chloroform for 120 minutes each on separate occasions (5 dogs, breathing augmented).

		2% Halothane	1% Chloroform
Systolic B.P.	B*	156	148
(mm Hg)	A†	98	110
Diastolic B.P.	B	102	106
(mm Hg)	A	81	78
Pulse rate	B	142	135
(/min)	A	99	118
Cardiac output	B	2.95	2.80
(bd. vol./min.)	A	1.95	2.24
Resp. rate	B	17	17
(/min.)	A	24	22
O_2 saturation	B	84	82
(%)	A	97	94
pH	B	7.32	7.30
	A	7.26	7.23
Plasma bicarb.	B	22.5	22.0
(mM/l)	A	23.0	21.2

* Before. †After

Electrocardiogram. In all experiments, arrhythmias were very uncommon. The heart rate decreased during the administration of halothane whether the animal was breathing spontaneously or with assistance. When breathing was augmented, chloroform caused only a slight reduction in the heart rate, whereas an increase in the heart rate was observed in most of the experiments in which breathing was spontaneous. These changes were seen whether or not the agent in question was administered first or second in the experiment. In none of the experiments was there a difference between the heart rate and pulse rate.

A decrease in the voltage and depression of the T wave was seen occasionally when the animals were breathing spontaneously. The only notable alterations in the electrocardiogram observed during anaesthesia were isolated ventricular extrasystoles. These occurred more frequently in the four dogs who were given 2 per cent chloroform for 2 hours than in any other group of animals in whom anaesthesia was given at a lower concentration and for a shorter duration.

One animal which breathed spontaneously during anaesthesia deserves special mention. It had occasional ventricular extrasystoles during the administration of 1.5 per cent chloroform for 90 minutes. These appeared frequently during the consecutive administration of 2 per cent halothane. At the subsequent experiment 6 weeks later, the animal died during the initial administration of halothane. On this occasion no gross arrhythmias were evident in the electrocardiogram. Terminally the electrocardiogram showed a marked decrease in voltage, progressive marked slowing of the heart rate and prolonged atrioventricular conduction time, and the polygraph tracings showed that there was severe hypotension. We feel that this fatal outcome was due to cardiovascular failure, but were unable to explain why this occurred.

CIRCULATORY AND RESPIRATORY EFFECTS

Spontaneous breathing. Summaries of the data derived from the individual experiments are shown in tables VII, VIII and IX. In the two

TABLE VII

Effect of 2% halothane and 1.5% chloroform for 60 minutes each on circulation and respiration (breathing spontaneously).

		2% Halothane	1.5% Chloroform	1½% Chloroform	2% Halothane	1½% Chloroform	2% Halothane	2% Halothane	1½% Chloroform
Systolic B.P.	B*	140	140	150	155	135	155	130	130
(mm Hg)	A†	100	100	75	95	100	90	90	110
Diastolic B.P.	B	85	90	105	105	90	115	90	95
(mm Hg)	A	55	50	50	60	65	50	40	85
Mean B.P.	B	103	107	120	122	105	128	103	107
(mm Hg)	A	70	67	58	72	77	63	57	93
Pulse pressure	B	55	50	45	50	45	40	40	35
(mm Hg)	A	45	50	25	35	35	40	50	25
Venous pressure	B	3	3	1	2	5	5	2	2
(mm Hg)	A	3	2	2	3	6	5	2	1
Pulse rate	B	96	90	116	120	65	114	82	76
(/min)	A	94	114	128	114	104	108	66	106
Cardiac output	B	2.58	—	1.96	—	1.66	—	2.08	—
(bd. vol./min)	A	2.15	2.00	1.72	1.41	1.08	1.63	1.07	1.42
Resp. rate	B	17	21	18	35	22	44	12	17
(/min)	A	16	41	42	27	27	22	8	30
Tidal volume	B	230	254	259	305	217	264	254	280
(ml)	A	181	149	108	173	259	197	188	243
Minute volume	B	3.92	2.34	4.14	10.7	6.3	11.6	3.05	4.76
(litres)	A	2.90	6.10	4.54	4.7	5.7	4.3	1.50	7.30

*Before †After

experiments of 1 hour duration (table VII) the only differences in response observed were a fall in pulse rate with halothane and a slight rise in pulse rate with chloroform. Breathing (tidal volume) was more depressed by chloroform than by halothane. Depression of blood pressure was similar for both agents, and was usually in excess of 25 per cent. In the animals under anaesthesia for 90 minutes and 120 minutes, the only obvious difference was the greater depression of respiration due to the administration of chloroform. This effect is not evident in the tabular data, because the periods in which apnoea ensued were not included in the analyses. Apnoeic periods requiring artificial respiration occurred much more frequently with chloroform than with halothane, and those which occurred occasionally with halothane appeared to be the result of a residual effect of the previous administration of chloroform in the same experiment. In these animals there was no consistent difference in the degree of blood pressure depression by the two anaesthetic agents, and it usually exceeded 35 per cent, especially after the 120-minute periods of anaesthesia (tables VIII and IX).

Augmented breathing. The degree of fall in blood pressure, pulse rate and cardiac output was slightly greater with halothane than with chloroform. The cardiac output fell gradually during administration of halothane anaesthesia. There was an initial rise in cardiac output with chloroform and then it fell as with halothane (tables VI and X and figs. 10 and 11).

The venous pressure did not change consist-

TABLE VIII

Effect of 2% halothane and 1.5% chloroform for 90 minutes each on circulation and respiration in dogs (breathing spontaneously).

		2% Halothane	1½% Chloroform	1½% Chloroform	2% Halothane	2% Halothane	1½% Chloroform	1½% Chloroform	2% Halothane	1½% Chloroform	2% Halothane	2% Halothane	1½% Chloroform	1½% Chloroform	2% Halothane	2% Halothane	1½% Chloroform	1½% Chloroform	2% Halothane*
Systolic B.P.	B†	140	130	140	120	135	145	130	135	125	130	120	115	130	145	130	125	150	110
(mm Hg)	A‡	95	100	110	90	130	90	60	70	95	100	75	100	105	100	90	75	100	100
Diastolic B.P.	B	95	90	95	65	95	105	90	95	85	80	85	85	85	85	90	85	115	65
(mm Hg)	A	60	70	60	55	90	65	40	40	50	55	50	60	60	50	50	50	60	70
Mean B.P.	B	110	103	110	83	108	118	103	108	98	97	97	95	100	105	103	98	127	80
(mm Hg)	A	72	80	77	67	103	73	47	50	65	70	58	73	75	68	63	58	73	80
Pulse pressure	B	45	40	45	55	40	40	40	40	40	50	35	30	45	60	40	40	35	45
(mm Hg)	A	35	30	50	35	40	25	20	30	45	45	25	40	45	50	40	25	40	30
Venous pressure	B	4	2	5	5	2	5	1	1	6	4	2	2	4	4	1	1	8	5
(mm Hg)	A	3	2	3	4	4	9	1	2	6	9	2	6	7	9	1	1	10	4
Pulse rate	B	126	110	102	140	120	128	102	146	122	174	130	112	116	110	118	86	124	160
(/min)	A	86	110	138	100	122	140	120	112	150	130	110	156	120	96	96	96	164	150
Cardiac output	B	2.32	—	2.78	—	2.73	—	2.02	—	2.86	—	3.30	—	3.30	—	2.11	—	2.19	—
(bd. vol. /min)	A	2.16	1.85	2.50	2.26	2.14	2.25	1.06	1.62	1.86	1.47	2.26	2.70	1.17	1.58	1.65	1.78	1.43	1.65
Resp. rate	B	22	27	21	42	15	20	10	32	19	32	26	32	20	30	22	18	15	38
(/min)	A	17	26	35	22	10	40	38	20	56	36	20	78	29	25	15	35	31	60
Tidal volume	B	245	226	248	213	251	159	278	123	112	125	219	104	195	376	219	93	313	97
(ml)	A	172	145	119	149	210	84	123	112	80	90	127	79	328	121	121	66	70	47
Minute volume	B	5.40	6 11	5.14	8.50	3.76	3.18	2.78	3.94	2.12	4.00	5.70	3.64	3.90	11.3	4.82	1.68	4.70	3.70
(litres)	A	2.92	3.20	4.16	3,28	2.10	3.34	4.67	2.24	4.50	3.24	2.54	6.13	9.50	3.02	1.82	2.30	2.18	3.05

*Died during halothane anaesthesia. †Before. ‡After.

TABLE IX

Effect of 2% halothane and 2% chloroform for 2 hours each on circulation and respiration in dogs (breathing spontaneously).

		2% Halothane	2% Chloroform	2% Chloroform	2% Halothane	2% Halothane	2% Chloroform	2% Chloroform	2% Halothane	2% Chloroform	2% Halothane	2% Halothane	2% Chloroform	2% Chloroform	2% Halothane	2% Halothane	2% Chloroform
Systolic B.P. (mm Hg)	B†	155	120	130	150	140	115	125	130	150	135	120	125	155	130	135	100
	A‡	80	150	55	100	90	90	95	85	110	110	85	95	95	85	80	80
Diastolic B.P. (mm Hg)	B	85	70	70	85	80	60	80	85	110	80	75	80	110	95	90	70
	A	40	65	25	45	45	50	40	45	65	55	40	45	55	50	50	55
Mean B.P. (mm Hg)	B	108	87	90	107	100	78	95	100	123	98	90	95	125	107	105	80
	A	53	93	35	63	60	63	52	58	80	73	55	62	68	62	60	63
Pulse pressure (mm Hg)	B	70	50	60	65	60	55	45	45	40	55	45	45	45	35	45	30
	A	40	85	30	55	45	40	35	40	45	55	45	50	40	35	30	25
Venous pressure (mm Hg)	B	9	4	4	4	6	2	2	2	4	11	2	2	6	6	4	2
	A	6	3	6	3	6	4	8	2	10	10	2	3	6	5	1	9
Pulse rate (/min)	B	104	100	94	100	98	94	110	114	138	160	180	100	140	128	174	110
	A	98	138	80	110	92	104	110	98	132	136	114	100	126	92	100	114
Cardiac output (bd. vol./min)	B	2.00	—	2.63	—	2.48	—	2.58	—	4.20	—	3.89	—	3.50	—	3.35	—
	A	1.81	2.12	2.08	2.40	2.13	2.20	1.24	1.92	2.76	2.28	2.60	2.22	2.34	2.98	2.44	1.96
Resp. rate (/min)	B	7	14	13	34	17	18	25	21	19	40	26	24	19	46	20	18
	A	12	31	47	31	13	22	8	19	27	29	29	34	9	10	10	26
Tidal volume (ml)	B	180	143	257	171	178	*	141	157	205	76	160	196	201	*	211	208
	A	106	71	94	116	108		104	175	91	84	94	100	127		216	105
Minute volume (litres)	B	1.26	2.00	3.34	5.83	3.00	2.50	2.40	3.30	3.90	3.04	4.17	4.71	3.82	*	4.22	3.75
	A	1.27	2.20	4.40	3.58	1.40	*	2.60	3.33	2.46	2.43	2.74	3.40	1.14		2.16	2.73

*Frequent occurrence of apnoea. †Before. ‡After.

TABLE X

Effect of 2% halothane and 0.8% chloroform for 90 minutes each on circulation and respiration in dogs with augmented breathing.

	Halothane		Chloroform		Chloroform		Halothane	
	Control*	90 minutes	Control	90 minutes	Control†	90 minutes	Control	90 minutes
Systolic B.P. (mm Hg)	150	119	144	120	150	120	151	120
S.D.	19	28	24	24	23	45	26	33
Diastolic B.P. (mm Hg)	103	79	99	82	104	78	102	74
S.D.	11	21	17	18	16	33	16	25
Mean B.P. (mm Hg)	119	92	114	95	119	92	118	90
S.D.	12	23	19	20	18	37	19	27
Pulse pressure (mm Hg)	48	40	45	38	47	43	49	47
Venous pressure (mm Hg)	3.8	4.7	3.3	4.9	3.6	4.2	3.1	2.4
Pulse rate (/min)	137	106	113	108	138	135	148	121
S.D.	22	33	44	20	11	40	44	45
Cardiac output (blood volumes/min)	2.98	2.26		2.03	2.94	2.09		2.01
Resp. rate (/min)	12	20	17	25	14	24	24	21
S.D.	4	5	3	4	4	3	8	4
Tidal volume (ml)	303	190	230	196	311	195	249	188
S.D.	160	48	40	26	106	39	84	50
Minute volume (litres)	3.64	3.80	3.91	4.90	4.35	4.68	5.98	3.96

*12 dogs. †10 dogs.

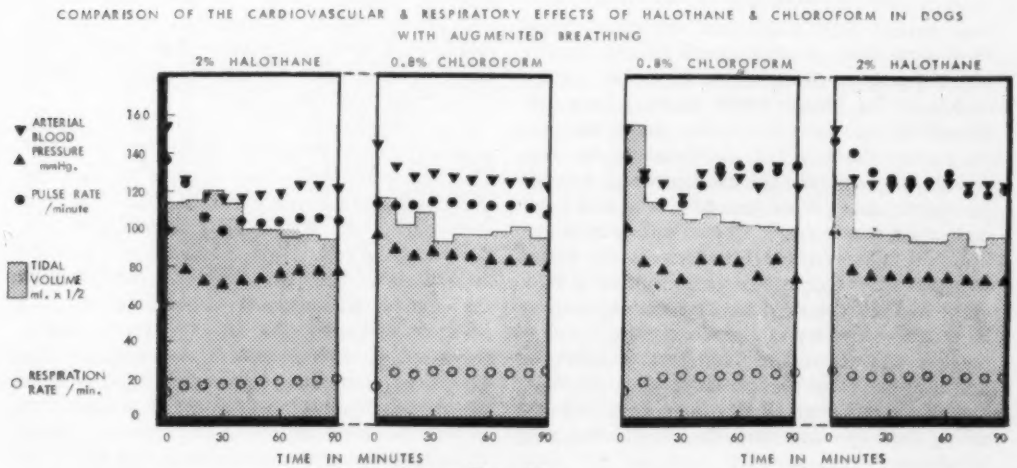

FIG. 10

Comparison of cardiovascular and respiratory effects of halothane and chloroform in dogs with augmented breathing.

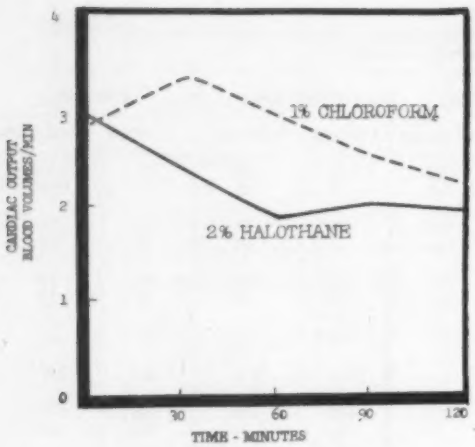

FIG. 11

Effect of 2 per cent halothane and 1 per cent chloroform for 2 hours on cardiac output (5 dogs, augmented breathing).

ently during the experiments, although there was a trend downward during halothane and an upward trend during chloroform when breathing was spontaneous, and an upward trend with both anaesthetics when breathing was augmented.

POSTANAESTHETIC CONDITION

Full recovery from anaesthesia was much slower when anaesthesia was continued for 90 minutes with either agent than after the 60-minute administrations. The animals which received 2 per cent chloroform recovered much more slowly than the others, but this was also attributed to the long periods of anaesthesia. The five dogs which received each agent once (2 per cent halothane and 1 per cent chloroform) for 2 hours with augmented breathing all recovered from anaesthesia within 2 hours after the experiments, so that neither agent by itself appeared to cause prolonged delay in return of full wakefulness. However, three of the five animals vomited and two of these did not take food for a few days after receiving chloroform, whereas all five dogs were well and taking food the day after the experiments with halothane.

Two dogs died 3 and 5 days *after* receiving consecutively 2 per cent halothane and 0.8 per cent chloroform for 90 minutes each, with breathing augmented. The cause of these deaths was not determined. Two deaths occurred *during* the administration of anaesthesia in the dogs that were allowed to breathe spontaneously. One of these died during the administration of 2 per cent halothane (vide supra). The other dog died during the administration of 2 per cent chloroform. Apnoea occurred and was inadvertently allowed to persist too long. The blood pressure was elevated and the electrocardiogram showed a rapid heart rate before the condition was discovered. By the time artificial respiration with 100 per cent oxygen was started, the blood pressure and pulse rate had fallen sharply, and continued downward until heart activity ceased. No attempt was made at cardiac resuscitation in these two dogs.

DISCUSSION

A few physicians quickly recognized the subtle and potent anaesthetic properties of chloroform immediately after its discovery and appreciated that it not only deserved but required to be handled with respect. For the most part they avoided anaesthetic deaths, even in thousands of administrations (Snow, 1858). Others, however, who administered it recklessly or less skilfully caused numerous deaths which resulted in the falling of an undeserved opprobrium on this agent. The formation of the various commissions to study this problem are historical evidence of the serious view taken of that state of affairs (B.M.A. Third Chloroform Committee, 1911).

The introduction of halothane as a general anaesthetic came at a much more opportune time. The 110 years which had elapsed between the introduction of chloroform and halothane had been accompanied by far-reaching improvements in the study and practice of clinical anaesthesia. The early users of halothane were all experienced in the art of administering anaesthetics and in addition to investigating the agent in the laboratory, they were meticulous in observing the vital signs in feeling the pulse, recording the blood pressure and maintaining a clear and unobstructed airway. In some instances they also monitored the electrocardiogram continuously in addition to their general observation of the patients (Bryce-Smith and O'Brien, 1956; Brennan, Hunter and

Johnstone, 1957). By contrast many of those who administered chloroform during the half-century following its introduction were quite casual in their observation of their patients. It is interesting to speculate what would be the prevailing opinion today if the order of introduction of these agents had been reversed.

Experimental difficulties.

It is difficult to compare halothane and chloroform reliably in a clinical study for two reasons. First, it is not feasible, nor justifiable, to subject human volunteers to a comparative experiment with anaesthetic agents with such potent pharmacological properties. It would, however, be justifiable to use agents in consecutive operations on the same patient. In order that such a study might give valid data for comparison, the nature of the operation would have to involve two similar procedures done at different times. Both operations too must be such that a considerable depth of anaesthesia would be necessary for a few hours; yet the procedures must not involve great surgical trauma, undesirable postures, profound muscle relaxation or considerable blood loss. Few have the opportunity to carry out a study of this kind because of the clinical limitations.

A comparison is far easier to arrange in animals. In the present experiments, however, other problems arose which could not be resolved in a manner which would make it possible to draw valid conclusions regarding the efficacy of chloroform and halothane from their results alone. For example, experiments could not show the difference between the powerful analgesic and muscle relaxant effects of chloroform and the weaker similar properties of halothane. There was also an obvious difference in hypnotic and respiratory sensitivity to these two agents both in dogs and in man. These points are of special importance and will be discussed more fully.

"Anaesthetic" potency.

The earliest animal experiments comparing the anaesthetic properties of the two agents were reported by Raventós (1956). He premedicated dogs with 2 to 3 mg/kg morphine and 0.5 mg/kg atropine (subcutaneously) 1 hour before, and inducted anaesthesia with thialbarbitone (Kemithal), 40 to 50 mg/kg intravenously. After a delay until signs of reawakening had appeared halothane induction was accomplished with 2 to 4 per cent to the point of surgical anaesthesia (loss of corneal reflex, predominantly abdominal respiration and muscle relaxation). Thereafter maintenance was possible with 1 to 2 per cent. He goes on to state, *on the basis of experiments with mice*, that halothane is 1.5 times more potent than chloroform. On the basis of the experiments reported here, using dogs, we must differ from Raventós' conclusions. In dogs, under the conditions described, chloroform is at least as potent as halothane as an anaesthetic—or, to be more specific, as a hypnotic and a respiratory depressant. Mørch and Jobgen (1959) found the same to be true in mice.

In man, our own experience has shown that the overall anaesthetic effect of chloroform (analgesia, hypnosis and muscle relaxation) is at least equal to that of halothane when the concentration administered was the same (0.4 to 1 per cent). At deeper planes of anaesthesia—e.g. for abdominal operations—one is inclined to administer a lower concentration of halothane (with nitrous oxide and oxygen) and more muscle relaxant (gallamine or suxamethonium halides) to avert circulatory depression (Dobkin, 1958, 1959). On the other hand, one may use a slightly higher concentration of chloroform (with nitrous oxide and oxygen) without requiring as much muscle relaxant (d-tubocurarine) (Dobkin, Johnston and Skinner, 1960).

We may, with some diffidence, draw the following conclusions as to the relative potency of the two agents. In man, under clinical conditions and using muscle relaxants, they are approximately equipotent. In dogs, premedicated with perphenazine and atropine, chloroform is more potent than halothane. In mice halothane is approximately as potent as chloroform. We may conclude further that *the dog*, which usually is tolerant of larger doses of analgesic-hypnotic drugs than man, *has a lower tolerance to chloroform than does man.* In the dog, in the absence of surgical stimulation, the inhalation of quite low concentrations of chloroform may result in apnoea. The administration of chloroform would be precluded if this was the case in man, unless one was prepared immediately to augment the pulmonary ventilation whenever apnoea occurred (Dobkin, Skinner and Johnston, 1960).

Halothane vaporized with oxygen does not produce steady unconsciousness in the dog until an inhaled concentration of 2 per cent is provided, although this dose may not always be sufficient for surgical manipulation. With 2 per cent halothane inhalation, dogs continue to breathe at a level of pulmonary ventilation which does not proceed to apnoea, even when the concentration is raised to about 3 per cent (Raventós, 1956; Dobkin, Harland and Fedoruk, 1960). In man, under clinical conditions, concentrations of less than 2 per cent may cause apnoea (Brennan, Hunter and Johnstone, 1957), sometimes without concomitant analgesia. We may conclude that *the dog is less sensitive to the hypnotic and respiratory effects of halothane than man, even when morphine is given for premedication.*

It is perhaps important to re-emphasize at this point that the experiments described above were performed with relative concentrations of the agents which were approximately equihypnotic. In both instances the concentrations were sufficient to render the dogs immobile and insensitive to the stimuli inherent in the experiments. One must interpret the effects upon the respiration, the cardiovascular system and on metabolism with this in mind.

Cardiovascular effects.

Serious cardiac arrhythmias may arise during chloroform or halothane anaesthesia and are greatly feared for obvious reasons (Embley, 1902; Levy and Lewis, 1911; Meek, 1941; Miller, Gilbert and Brindle, 1958). These can be virtually eliminated by assuring adequate pulmonary ventilation, avoiding the administration of catecholamines, controlling the administered concentration of the vapour to a level which is safe, and by using suitable premedication which depresses excessive autonomic responses by the heart (Waters, 1951; Brindle, Gilbert and Miller, 1957; Armstrong Davison, 1959; Dobkin and Purkin, 1959; Dobkin, Donaldson and Purkin, 1959).

When conditions were arranged so that myocardial irritability was not a major consideration, by protecting the animal with atropine and perphenazine, and when breathing was augmented, the concentration of chloroform which maintained steady unconsciousness (0.8 to 1 per cent), and indeed even when the inhaled concentration was higher (1.5 to 2 per cent), the blood pressure or the cardiac output was not depressed to any greater extent than was the case when 2 per cent halothane was used.

In the five animals (experiment 5D) which received each anaesthetic for 2 hours on different occasions, the cardiovascular effects were more obvious. Halothane (2 per cent) caused a progressive lowering of the blood pressure, pulse rate and cardiac output throughout most of the period of its administration. Chloroform (1 per cent), on the other hand, initially tended to elevate the blood pressure, pulse rate and cardiac output, and then a depressant effect similar to that of halothane became evident. Although Blalock (1928) did not control the vapour concentration of chloroform in his studies on dogs, he administered enough by an open cone to secure general relaxation and abolition of the lid reflex. In his estimations on fifteen dogs, there was a decrease in cardiac output that varied from zero to 50 per cent, with an average of 28 per cent. During the experiments he observed that the pulse rate was usually increased and the blood pressure decreased to a moderate degree. These observations are essentially the same as those reported here in the dogs which were allowed to breathe spontaneously. It was interesting to find also that the changes in cardiac output observed with chloroform in dogs were similar to those reported with intravenous pentobarbitone anaesthesia (Howell and Horvath, 1959).

The necessarily limited information derived from human experimentation indicates that in normal children and adults, the depression of cardiac output and other cardiovascular signs caused by halothane are of a similar nature to that noted here with dogs (McGregor et al., 1958; Wyant et al., 1958). Under clinical conditions, with the usual adjuvant measures, our experience has been that neither agent ordinarily has much effect upon cardiovascular homeostasis (Dobkin, 1958; Payne, Gardiner and Verner, 1959; Dobkin, Skinner and Johnston, 1960).

Alterations in arterial blood pressure and cardiac output usually paralled changes in the contractile force of the heart. Although the latter was not measured in these studies, Boniface, Brown and Kronen (1955) have shown that when chloroform is administered to dogs to the stage

of apnoea, the contractile force of the heart is reduced to almost 25 per cent of control values. Myocardial recovery is slow after chloroform anaesthesia because it is practically devoid of the sympathoadrenal stimulant response which is seen with an agent such as diethyl ether (Boniface, Brown and Kronen, 1955). Others have shown that a similar decrease in contractile force of the heart occurs during such experiments with halothane, and is accompanied by severe hypotension and sinus bradycardia (Thrower et al., 1960).

Price and his associates have shown that halothane anaesthesia causes little or no sympathoadrenal response, which may account for the more marked depression of blood pressure than is seen with cyclopropane, thiopentone and diethyl ether (Price et al., 1959; Price et al., 1960). On the other hand, Miller and Morris (1960) found that 2 per cent halothane in dogs, with breathing augmented, did not significantly reduce the sympathoadrenal response to hypercarbia, caused by adding 10 or 20 per cent carbon dioxide to the oxygen-halothane anaesthesia, although there was probably some depression of the sympatho-adrenal response to graded haemorrhage.

Metabolic effects.

Even though halothane appeared to have a greater propensity to raise the serum potassium level than did chloroform, it is probably unjustifiable to interpret this response as indicative of a greater depressant effect on the heart (Bellet, 1955). It may, however, be related in some way to the electrocardiographic changes that are seen during the clinical administration of halothane (Brennan, Hunter, and Johnstone, 1957; Miller, Gilbert and Brindle, 1958; Dobkin, 1958). Other than this relative tendency for halothane to cause a slight hyperkalaemia, electrolyte estimations do not serve to differentiate the two agents.

Chloroform caused a rise in the blood sugar in most of the dogs when breathing was not augmented. This response is probably due to the glycogenolytic effect of chloroform on the liver, a characteristic not evident with halothane. After reviewing some of the published studies regarding hepatotoxicity of these two agents, we noted that in many of the experiments ventilation was neither monitored nor augmented. Previous data must be re-interpreted in this light (Dobkin, Skinner and Johnston, 1960). As shown in this study, the dog is easily rendered apnoeic with chloroform and the glycogenolysis thus caused may well be a relevant factor in any hepatic impairment which subsequently becomes manifest. This effect seems less likely with halothane.

The cephalin cholesterol flocculation test was selected from several that can indicate hepatocellular damage. With both agents, changes of approximately the same magnitude (slight) were observed in this test and these were not progressive. Other recent work also indicates that chloroform is no more hepatotoxic than are the other halogenated anaesthetics. Furthermore, experimental results using animals that indicate some hepatocellular toxicity, should not be interpreted as necessarily implying a like toxicity in the human under clinical conditions (Waters, 1951; Little, Barbour and Given, 1958; Morris, 1960).

Even after 2 hours of anaesthesia with chloroform or halothane, the oxygen saturation of the blood was within normal limits, so that one need not fear tissue hypoxia, provided that adequate pulmonary ventilation is ensured. Smith (1960) has shown that neither agent has any influence on the oxygen dissociation curve of human blood. There is no reason to believe this is not so in dogs also. Since there was little or no change in the haematocrit with either agent, one may conclude that they do not by themselves cause haemoconcentration of the blood.

The fall in pH of the blood during spontaneous breathing is similar with halothane and chloroform, but the change with halothane is accompanied by a slight rise in plasma bicarbonate, whereas that with chloroform is accompanied by a slight fall in plasma bicarbonate. This difference might indicate that chloroform causes a somewhat greater metabolic disturbance. Since the rise in arterial carbon dioxide tension was of the same order of magnitude for both chloroform and halothane, and apnoea was much more likely with chloroform, it appears also as if halothane does not depress the respiratory response to an elevated arterial Pco_2 as much as does chloroform in dogs (Schmidt and Harer, 1923; Whitteridge and Bulbring, 1946). This difference might be even more obvious if the animals were premedicated with a narcotic such as morphine. In clinical practice, these observations are not so important because

it is usually necessary to augment pulmonary ventilation regardless of which agent is used, particularly if premedication with a narcotic (e.g. morphine) is used (Brennan, Hunter and Johnstone, 1957; Shearer, 1960).

The story relating the use of chloroform in Scotland (and England) has been scrutinized minutely by Sykes (1960) with perhaps a little more derisive prejudice than it deserves. The lesson of history tells, if nothing else, that chloroform should not be doled out in capsules for use by the unqualified, and its potency warrants all the care and attention that modern anaesthetists consider essential to proper patient care during anaesthesia with any potent anaesthetic agent. It took only a few months to realize the same thing with halothane! At one teaching centre in the United States, halothane was not used with due caution initially and was precipitately dropped, not to be re-appraised until almost four years had elapsed. Misuse of the azeotropic mixture of halothane and diethyl ether has resulted in similar feelings of apprehension (Johnstone, Evans and Murphy, 1961). We cannot with any certainty predict when the exact position of chloroform as a general anaesthetic will be settled. The stormy course which was to mark the story of chloroform's acceptance is adumbrated by the letter to the editor of *Lancet*, written by John Snow (January 27, 1855) and quoted in its entirety by Sykes, which sums up the clinical efficacy of chloroform exceedingly well. This letter is worth reading even now by everyone who contemplates using chloroform for general anaesthesia. Armstrong Davison (1959) has more recently echoed Snow's sentiments in a modern way. While holding no brief for chloroform as an anaesthetic agent we would like to quote some authorities who have spoken in its defence. John Gillies stated in 1948: "That chloroform still has a place in anaesthetics, even though that may be a small one, is undoubted. The need of it would appear to apply more to the general practitioner than to the specialist, but what the general practitioner requires is certainly the concern of the teaching anaesthetist." In 1950 Corkill concluded an indignant plea against censuring the use of chloroform in obstetrics with the following:

> A strong protest is entered against the creation of a medicolegal position in which the user of chloroform is prejudiced in the event of accident. Those who are convinced of the great value of chloroform in obstetrical practice are just as zealous for the well-being and safety of their patients as those who think otherwise, and just as jealous of their reputation and standard of practice. They do not seek to force their opinion on others but claim the right to exercise their own judgment in this matter and without prejudice.

The monograph on chloroform from Madison, Wisconsin, supports those opinions (Waters, 1951). Those who fear using chloroform may wonder how such statements could be made almost 40 years after the Committee on Anaesthesia of the A.M.A. stated in 1912 that "the use of chloroform for major operations is no longer justifiable".

All these statements were made prior to the advent of halothane. We can only speculate how these authors would feel if they had gained the same experience with halothane which they had accumulated with chloroform. It may be that after finding the newer agent had some advantages, such as allowing more rapid recovery and causing less postoperative vomiting, they might no longer number themselves as advocates of chloroform (Cutter and King, 1960). However, as recently as March 1960, Dr. Armstrong Davison wrote to one of us:

> I believe that, in careful hands, chloroform is a safe drug to use; if I did not believe this, I should have given up its use long ago. As it is, I scarcely ever give an anaesthetic without administering at least some chloroform, although the cases in which I use it as the main agent are comparatively rare. At the same time I do not believe that chloroform should be used by the beginner nor by people whose judgment is likely to be faulty. The responsibility is so immediate, and the consequences of an overdose so drastic, that it must never be administered save when a competent anaesthetist is able to give his complete attention to the whole administration. I think it probable that much help can be derived from various instruments, for example, e.c.g. tracings, cardiotachometer, continuous blood pressure recordings, and the rest; however, I also believe that clinical appreciation is of greater importance in determining the safety of the patient than is the inspection of dials of electronic apparatus. The latter are not always in perfect functioning order, and failure to see an expected complex may lead to tampering with the machine instead of attending to the patient, thus losing valuable seconds. This, of course, is one of the main problems of anaesthesia today. I suppose I am old-fashioned, but it is my feeling that, in teaching the postgraduate student we nowadays place too much reliance upon mechanical aids, and insufficient emphasis on the clinical condition of the patient.

It is interesting to note that the same advice was expressed in this journal in a comment on the safe use of halothane (Wyant, 1960).

On the basis of the experiments reported here, one may surmise that halothane is perhaps a little more safe from the respiratory and metabolic aspect. To use chloroform with the same safety may require that little bit of extra skill and judgment that often makes the clinical difference felt, but difficult to identify. There is no doubt that both agents can only be given safely when administered by an experienced clinician. Management of the anaesthetic is facilitated by using an accurate metering device. General use of the latter would be a great step forward in the safe administration of all the potent inhalation anaesthetics.

If the matter of expense of halothane and chloroform was the only consideration, the choice would weigh heavily on the side of chloroform. Where cost is not a primary factor, it is easier and perhaps safer to provide the extra money rather than greater skill. In many parts of the world, on this alone may rest the final choice between chloroform and halothane, until a new potent nonexplosive anaesthetic vapour is discovered which costs less or requires much less skill to administer.

SUMMARY AND CONCLUSIONS

Preliminary experiments showed that dogs were more sensitive to the respiratory and hypnotic effects of chloroform than to halothane. Anaesthesia with halothane (2 per cent) and chloroform (0.8 to 2 per cent) were then compared under the same conditions during spontaneous and augmented breathing in twenty-nine dogs. Cardiovascular and respiratory parameters were monitored continuously while each agent was administered for 60, 90 and 120-minute periods of anaesthesia. Cardiac output estimations and tests of anion-cation balance, electrolyte balance, haematocrit, blood glucose and cephalin cholesterol flocculation were done before and after each anaesthetic.

The cardiovascular response to these two agents was of the same order of magnitude except that the depression of the blood pressure, pulse rate and cardiac output occurred sooner with halothane than with chloroform. At the end of 2 hours of anaesthesia, there was little difference in the cardiovascular response to these two agents, even when administered in the same concentration. No serious cardiac arrhythmias were observed during the administration of either agent. This was attributed partly to premedication with perphenazine and atropine, to control of the administered vapour concentration, and to adequate oxygenation during the experiments.

Both agents caused a progressive respiratory acidosis when breathing was not augmented. Chloroform caused a slight tendency to metabolic acidosis, which was not seen with halothane.

A rise in the blood sugar usually occurred with chloroform but this could be averted by augmenting the breathing. This change was not seen with halothane, even when breathing was spontaneous. The cephalin cholesterol flocculation test became positive with both anaesthetics, but did not progress during the course of an experiment. This indicates that the liver is sensitive to the effects of both chloroform and halothane, as it is to most potent anaesthetic agents.

Halothane caused a rise in the serum potassium, the exact cause of which remains obscure. It may, however, predispose to myocardial depression and perhaps serve to explain some of the changes seen in the electrocardiogram during clinical anaesthesia with halothane.

Both agents probably lack the ability of diethyl ether to provoke a marked sympatho-adrenal response to hypercarbia and haemorrhage. Whether or not this is a useful characteristic cannot be answered unequivocally.

The more prolonged recovery time and the increased incidence of postoperative vomiting with chloroform, as compared with halothane—which are a matter of common clinical experience and were reproduced during this study—are probably related to the greater degree of metabolic imbalance induced by chloroform and may be related also to its more potent hypnotic and analgesic properties. Severe respiratory depression is also more likely with chloroform. On the other hand, halothane causes somewhat greater cardiovascular depression and a rise in serum potassium. Should these changes occur in the same way in man, the clinical anaesthetist would have to pay greater attention to the breathing during chloroform and greater attention to the circula-

tion with halothane. In the patient who has already a major metabolic disturbance halothane might be the better choice, but perhaps halogenated compounds should be avoided altogether in such cases, unless an inhalation anaesthetic is desirable and unless the surgeon must use the cautery to facilitate his operation.

As emphasized earlier, the results noted cannot be applied without qualification to clinical practice. They do, to some degree, serve to confirm a pre-existing opinion that neither of these agents possesses tremendous advantages over the other, provided appropriate precautions are taken. However, we remain of the opinion that chloroform demands a little more skill than halothane in clinical use and that only where cost is a prime consideration should chloroform be the agent of choice.

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ANAESTHETIC AND POSTOPERATIVE HAZARDS IN RHEUMATOID ARTHRITIS

BY

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RHEUMATOID arthritis remains a common and incurable disease of unknown cause. Because of its great frequency (Kellgren and Lawrence, 1956) patients often present with incidental surgical disorders; alternatively, they require consideration for remedial or palliative orthopaedic surgery (Bastow, 1955). It is therefore important that those characteristics of rheumatoid arthritis which may lead to unexpected anaesthetic or postoperative difficulties should be widely appreciated. However, little attention has been paid to this aspect of the disease. The purpose of this paper is to describe a group of patients in whom postoperative death or extreme respiratory difficulty during anaesthesia were wholly or partly attributable to the articular and systemic changes of rheumatoid arthritis.

Case 1.

A female, aged 42, had suffered from rheumatoid arthritis for 20 years and was admitted to hospital for arthroplasty of the right elbow. All diarthrodial joints were apparently involved; she had been confined to bed for 10 years, suffering from recurrent episodes of respiratory infection including seven attacks of lobar pneumonia, each responding to antibiotic treatment. Laryngeal stridor had been noticeable for 5 years but had caused no subjective distress. Respiratory efficiency was impaired by ankylosis of the costovertebral joints with almost complete immobility of the thoracic cage. For 4 years she had been known to have diabetes mellitus.

After premedication with morphine 10 mg and atropine 0.6 mg, anaesthesia was induced with thiopentone 250 mg and maintained with cyclopropane and oxygen. Endotracheal intubation was found to be impossible. The larynx could not be seen because of ankylosis in flexion of the cervical vertebrae and greatly diminished mobility of the temporomandibular joints. Attempts to intubate blindly failed, possibly because of laryngeal stenosis. However, the insertion of a nasopharyngeal tube resulted in satisfactory respiratory excursions.

For a little more than 1 hour progress was satisfactory; thereafter increasing respiratory obstruction developed. With the appearance of cyanosis, and after a further attempt at tracheal intubation had failed, laryngostomy was performed by transverse incision through the cricothyroid membrane and the distal end of a No. 7 endotracheal tube inserted. The tube was then cut and connected to the anaesthetic machine and the operation completed after a further 20 minutes. Tracheostomy was not attempted because of the flexion deformity of the neck. A metal tracheostomy tube was substituted for the rubber catheter at the end of the operation.

The patient regained consciousness rapidly and remained a good colour without oxygen therapy. Physiotherapy was started on the day following operation and frequent tracheal toilet carried out. The laryngostomy tube was removed after 2 days; within 3 weeks the opening had healed. Because there had been some urgency, laryngostomy had been performed with unscrubbed hands but by the "no-touch" technique; local infection was slight. Postoperative progress was uneventful except for copious tracheobronchial secretion for a few days. The patient was referred to a laryngologist who failed to see the larynx, directly or indirectly.

Case 2.

A female, aged 33, had suffered from rheumatoid arthritis for 21 years. She was admitted to the oral surgical unit for mobilization of the mandible. Rheumatoid arthritis was severe; all diarthrodial joints were apparently involved. A right mandibular condylectomy had been performed 10 years previously. Nevertheless the patient was now able to open her mouth only 1.25 cm. The cervical vertebrae were ankylosed in flexion. There was respiratory difficulty and stridor.

After premedication with atropine 0.6 mg, cyclopropane and oxygen anaesthesia was induced by facepiece and maintained by nasopharyngeal tube. Excision of 1 cm of the ascending ramus of the right mandible was performed; the patient recovered consciousness shortly after the end of the operation. Eight hours later she was given papaveretum (Omnopon) 20 mg because of restlessness. Two and a half hours later she was found to be dead.

Necropsy. The body was that of a deformed young female. The principal limb joints, including those of the fingers and toes, and the joints of the cervical region were ankylosed. There was spindle-shaped deformity of the digits, and a generalized wax-like appearance of the skin. The skeletal muscles were atrophic and

extensively replaced by fat. A recent unhealed surgical incision indicated the site of division of the right ascending mandibular ramus. The heart was small and atrophic (270 g). The coronary arteries were free from atheroma but there was severe atheroma of the abdominal aorta. Small serous effusions were present in both pleural cavities. The lungs, conspicuously pale, were collapsed and slightly oedematous. The larynx was preserved unopened for fixation. The liver was small and pale but neither in it nor in the kidneys, small intestine or spleen was amyloid demonstrable. The spleen was enlarged to twice normal in size; on the cut surface was a prominent follicular pattern. Generalized enlargement of lymphoid tissue in other regions was not recognized. The kidneys were small with coarse cortical scarring. Numerous small irregular calculi were present in both renal pelves and in the calyces; they were associated with severe generalized osteoporosis and with acute bilateral pyelonephritis. Parathyroid hyperplasia was not recognized.

Microscopically, no amyloid was found. Rheumatoid arthritis of the small joints of the larynx was active and severe (figs. 1, 2, 3). The synovia of the crico-arytenoid joint was hyperplastic. This joint and the surrounding para-articular connective and muscular tissues were extensively infiltrated by aggregates of plasma cells. Similar cells lay in marginal lacunar erosions in the laryngeal cartilages and within the medullary cavity of the bone formed in the centre of these cartilages. Comparison with the larynx of a normal female of the same age confirmed that ossification was excessive in amount and emphasized the severity of lymphoid hyperplasia. The superficial margins of the cartilages within the crico-arytenoid articulation were replaced by cellular pannus; similar incomplete replacement fibrosis involved the marrow cavity. Acute and chronic pyelonephritis were confirmed. There was incomplete pulmonary atelectasis. The lymph nodes contained many plasma cells and Russell bodies.

Death was attributed to mechanical respiratory difficulty, during and after anaesthesia, caused by thoracic immobility and by rheumatoid arthritis of the larynx and resulting in partial collapse of both lungs. Impaired renal function due to pyelonephritis and nephrolithiasis was a significant contributory cause.

Case 3.

A female, aged 67, was admitted to hospital 4 hours after the neck of the right femur had been fractured during a fall. She was found to have moderately advanced rheumatoid arthritis of both hip and knee joints but clinical examination revealed no other significant disease. The fracture was reduced on the evening of admission and fixed by a Smith-Petersen nail.

After premedication with papaveretum (Omnopon) 10 mg and atropine 0.6 mg anaesthesia was induced with thiopentone 150 mg and gallamine 60 mg and was maintained with a nitrous oxide and oxygen mixture with the occasional addition of trichloroethylene through an orotracheal tube. The patient regained consciousness shortly after the end of the operation but was found to be slightly cyanosed. Examination of the blood revealed sulphhaemoglobinaemia. One litre of packed red blood cells was given. On the following day she developed severe

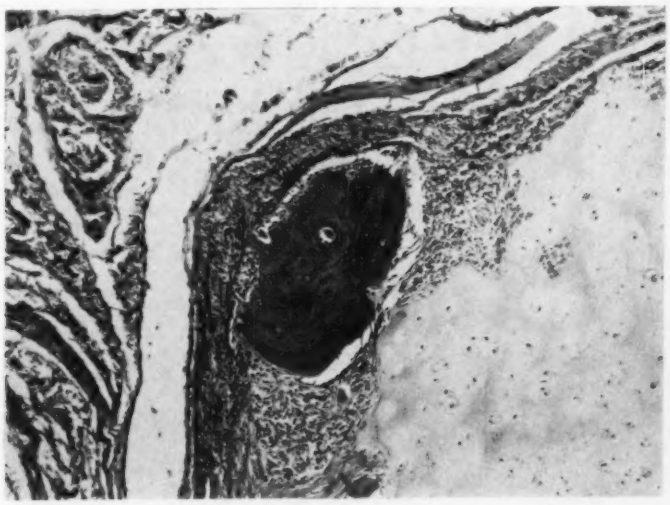

FIG. 1

Case 2. Margin of crico-arytenoid joint; ossification has occurred within the cricoid cartilage. Both synovia and cartilage are extensively infiltrated with inflammatory cells. Haematoxylin and eosin. × 70.

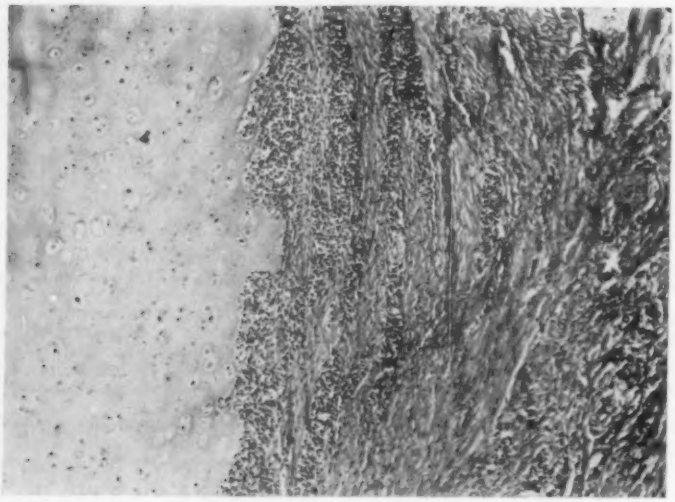

FIG. 2

Case 2. Perichondral connective tissue adjoining cricoid cartilage infiltrated by inflammatory cells which are associated with lacunar absorption of the cartilage. Haematoxylin and eosin. × 70.

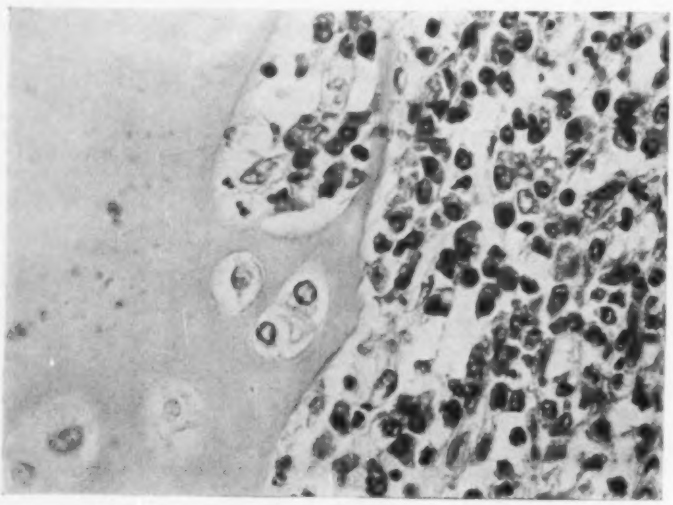

FIG. 3

Case 2. Same field as fig 2. The majority of the infiltrating cells are plasma cells. Haematoxylin and eosin ×575.

diarrhoea, a remittent pyrexia and paroxysmal tachycardia, rate 180/minute. Quinidine sulphate was prescribed. In spite of this her condition deteriorated over the next 4 days and rapidly deepening jaundice developed. Coma was followed by death 6 days after operation.

Necropsy. The body was that of a well-nourished elderly female. There was severe jaundice. Occasional small ecchymotic haemorrhages were scattered over the skin of the trunk. The unhealed scar of the recent operation was present over the right hip joint. The characteristic deformity of rheumatoid arthritis was shown by palmar flexion of the wrist joints and fusiform swelling and ankylosis of the metacarpophalangeal and interphalangeal joints. The right knee joint contained 150 ml of grumous fluid and was the site of severe secondary degenerative joint disease.

The liver was mottled yellow and brown and was significantly enlarged (1720 g). Many gas bubbles were present on the cut surface and accounted for a disproportionate increase in size relative to weight. The spleen was much enlarged (490 g), purple-black and exceptionally soft. Diffluent bone marrow occupied the proximal half of the right femoral marrow cavity, the vertebrae, ribs and sternum. Extreme generalized enlargement of lymph nodes was present; the nodes in the axillae measured up to 3 cm in diameter, with uniform, grey-purple cut surfaces. There was slight coronary artery atheroma but minimal atheroma of the aorta. Antemortem thrombus was present in the calf veins of both legs. Blood-stained fluid lay within the pericardial sac. There was an acute purulent bronchitis. The pituitary was deeply bile-stained.

Microscopy revealed clusters of Gram-positive bacilli within the connective tissue septa at the site of the wound and around the margins of gas bubbles within the greatly distorted liver lobules. There was no evidence that pre-existing liver disease could have contributed to the progressive jaundice. Many Gram-positive organisms were within the femoral bone marrow; the variegated marrow appearance was the result of focal necrosis. Other Gram-positive bacteria were seen within mesenteric blood vessels. The enlarged lymph nodes showed only the extreme follicular hyperplasia characteristic of rheumatoid arthritis. By contrast the congested spleen contained few bacteria and showed little evidence of follicular hyperplasia. In the kidney there was necrosis of both proximal and distal convoluted tubules. The presence of sulphhaemoglobin was confirmed in blood taken at necropsy.

Death was attributed to an anaerobic bacterial infection apparently arising in relation to the recent surgical incision and leading to progressive liver cell destruction. The presence of widespread lymphadenopathy, with splenomegaly, osteoporosis and arthritis suggested that the patient's resistance to infection might have been impaired and that sulphhaemoglobinaemia, caused by drugs, might have been sufficient to allow the rapid and unexpected proliferation of Clostridia. The possibility that these anaerobic organisms had been present within the knee joints before the accident occurred could not be excluded.

Case 4.

A male, aged 55 years, was admitted for acrylic arthroplasty of the right hip joint. He had suffered from rheumatoid arthritis for 10 years. The disease had started in the joints of the hands and had gradually affected the shoulders, hips, knees and ankles. Hydrocortisone had been given, followed on each occasion by periods of remission. Nevertheless progress of the disease was inexorable and rapid. The third, fourth and fifth cervical intervertebral joints were implicated but the temporomandibular joints were apparently intact. Seven months previously a successful arthrodesis of the right knee joint had been performed. He was known to have had a gastro-enterostomy 30 years previously. His general health at the time of admission for arthroplasty of the right hip joint was good, although there were occasional complaints of unexplained dysphagia and epigastric discomfort.

After premedication with morphine 10 mg and atropine 0.6 mg anaesthesia was induced with thiopentone 500 mg and gallamine 80 mg, maintained with cyclopropane and oxygen through an orotracheal tube. To minimize bleeding hypotension was induced with hexamethonium bromide 50 mg. His progress during and immediately after operation was uneventful; the blood pressure was normal within 2 hours after his return to the ward. Twenty-four hours later he developed the signs and symptoms of paralytic ileus followed by those of peritonitis. He died 4 days after the operation following an emergency laparotomy at which a ruptured jejunum was found.

Necropsy. The body was that of a well-nourished middle aged male. A fully healed linear scar extended over the lateral aspect of the right leg in the region of the knee joint and an incompletely healed linear scar ran vertically downwards over the lateral aspect of the right hip joint. A more recent paramedian incision was present; there was generalized abdominal distension. The right knee was ankylosed, the left retained slight mobility. Characteristic, but slight rheumatoid deformity of the small joints of both hands, but not of the feet, was present.

There was generalized acute peritonitis. Loops of bowel were bound loosely together by a thin fibrinopurulent exudate. The reaction centred about the root of the mesentery beneath which the site of the old, intact gastro-enterostomy was found. Two cm distal to the anastomosis on the right lateral wall of the jejunal loop was a large, active, chronic peptic ulcer of bifid form. The upper, more posterior part of this ulcer had eroded backwards into the pancreas; the lower part had perforated.

There was slight coroffary artery atheroma. The inferior vena cava and renal veins were free from thrombus. Both kidneys were unusually pale, weighing 165 g each; the external surfaces were finely granular. Part of the pleural cavities overlying the lower lobes of both lungs were obliterated by fibrous adhesions; the lungs were congested and oedematous (right 650 g, left 600 g). The spleen was significantly enlarged (175 g); on its divided surface lymphoid follicles were easily seen. Lymph nodes in all parts of the body were enlarged.

Microscopic examination confirmed acute peritonitis. Both kidneys, the suprarenals, the spleen and the small intestine were involved by severe amyloidosis of secondary distribution; there was ischaemic renal tubular atrophy. Small, recent emboli were present in the pulmonary arterial branches. The spleen was congested but contained less iron than normal; the lymph nodes showed conspicuous sinus cell hyperplasia and contained much iron. Many small

petechial haemorrhages were present in the internal capsules of the brain. In one suprarenal there was a small cortical adenoma. The bone marrow was actively haemopoietic, the plasmacytosis of rheumatoid arthritis being readily recognized

It was concluded that, while death was the immediate result of acute peritonitis, following perforation of an unsuspected stomal ulcer, and of pulmonary emboli, with ischaemic cerebral haemorrhages, the response of the patient to anaesthesia and surgical intervention had been prejudiced by the severe widespread amyloid disease, with corresponding impairment of renal function, and by the anaemia which accompanied active rheumatoid arthritis.

Case 5.

A female, aged 51 years, was admitted for operative correction of bilateral hallux valgus. She had suffered from rheumatoid arthritis for 19 years; the disease was limited and apparently quiescent. There was no involvement of the cervical vertebrae or of the temporomandibular joints, and she did not complain of respiratory difficulty. Her general health was good. Only the first metacarpophalangeal joints were painful.

After premedication with morphine 10 mg and atropine 0.6 mg anaesthesia was induced with thiopentone 400 mg and maintained with cyclopropane and oxygen. An oral airway ensured unimpeded respiration throughout the operation which lasted 50 minutes. She was returned to the ward in a state of good oxygenation, breathing satisfactorily and having regained reflex activity. Fifteen minutes later the anaesthetist was called to the ward and found the patient dead.

Necropsy. The body was that of a well-nourished middle-aged female. The characteristic rheumatoid deformity of the digits was present. The incisions for the recent arthroplasties were identified. There was incomplete collapse of the lower lobe of the left lung, but the bronchi contained no inhaled material. The trachea and larynx were substantially normal; the larynx was not preserved for section. Slight hypertrophy of the left ventricular myocardium was associated with atheroma localized to a zone in the anterior descending branch of the left coronary artery 2 cm distal to its origin. The cardiac valves and septa were intact. Congestion of the dark, red-brown liver and of the small, firm spleen were associated with an intact gastro-intestinal system. The kidneys were firm and of normal size with smooth external surfaces from which the capsules stripped readily; the medulla and cortex on each side were clearly defined. There was slight oedema of the brain shown by the presence of gyral flattening but uncal herniation and cerebellar coning were not recognized. The blood vessels of the medulla and of the internal capsules were congested; infarction was not detected.

Microscopy confirmed the presence of incomplete patchy collapse of the lower lobe of the left lung. Examination of representative blocks of tissue from the myocardium, cerebral cortex, the basal ganglia, internal capsules, medulla, liver, suprarenals, kidneys and spleen failed to reveal a satisfactory histological explanation for death which, in the absence of more adequate evidence was attributed to asphyxia. In particular it was observed that there was no evidence of systemic amyloidosis or of unsuspected infection.

DISCUSSION

The clinical manifestations of rheumatoid disease may be considerably less obvious than the pathological. It is not widely appreciated that the visceral lesions of rheumatoid arthritis (Ellman and Ball, 1948; Bevans et al., 1954; Sinclair and Cruickshank, 1956) and the unexpected inflammation of small joints, such as those of the larynx, may present difficult problems to anaesthetists dealing with patients undergoing operation for some coincidental disease or in those patients in whom surgical relief is sought for disability resulting from the arthritis.

In the present account the cases of five patients are reported in which unexpected difficulty in management was wholly or partly attributable to the rheumatoid disease from which they suffered. In cases 1 and 2 respiratory difficulty was caused by rheumatoid arthritis of the small joints of the larynx and by ankylosis of the costovertebral joints. Arthritis of the larynx is now a well-recognized but inconstant feature of the disease (Copeman, 1957; Baker and Bywaters, 1957; Pearson, 1957; Copeman, Elkin and Pearce, 1959). It may be accompanied by rheumatoid lesions in the pleura and heart (Gresham and Kellaway, 1958). That these lesions may cause respiratory difficulty in connection with anaesthesia has not been reported previously. Such respiratory dysfunction would seem to be particularly likely to cause death in those patients with pre-existing lung disease; as Cruickshank (1959) has indicated, the tendency for interstitial pneumonia to develop in rheumatoid arthritis is sufficiently frequent for it to be regarded as a characteristic of the disease. In other instances stridor may be the result of a neuropathy affecting the laryngeal muscles and occasionally associated with rheumatoid arthritis (Darke, Wolman and Young, (1958).

The possibility of respiratory inadequacy when surgical intervention is undertaken in subjects with rheumatoid arthritis may be anticipated when there are signs of laryngeal involvement, when there is limitation of movement of the thoracic cage, often with ankylosis of the costovertebral joints, and when the temporomandibular joints are implicated. For these patients regional analgesia offers greater safety than general anaesthesia. This is especi-

ally so when laryngeal arthritis is known to be present. It should be remembered that tracheal intubation is often impossible in these circumstances. When the site of operation makes regional block impracticable, pre-operative tracheostomy or laryngostomy may have to be considered. The latter will be preferred when severe flexion deformity of the cervical spine is present because the opening is required only for the operative and immediate postoperative period.

Case 2 illustrates in addition the extreme sensitivity of these patients to agents which depress respiratory function. Although this is principally the result of impaired mobility of the larynx and thoracic cage, it places in question the efficiency with which patients with rheumatoid arthritis metabolize such drugs. In Case 3, the finding of sulphhaemoglobinaemia was attributed to analgesic drugs which the patient had been taking before admission to hospital.

In Case 4, in whom subsequent necropsy revealed severe amyloidosis, undetected impairment of renal function may have been a factor contributing to delayed excretion of the hexamethonium used during anaesthesia. Paralytic ileus, possibly induced by the hexamethonium (Douthwaite and Thorne, 1951), may have led to undetected perforation of an active but silent stomal ulcer, whose activity may be attributed to prior treatment with hydrocortisone. Amyloidosis of sufficient severity to lead to extensive renal damage has been found in eight of the fifty necropsies on patients with rheumatoid arthritis collected by one of us (D.L.G.). In association with the anaemia which is characteristic of the disease (Richmond et al., 1956) impaired renal function may always be a factor in determining the altered response of patients with rheumatoid arthritis to agents used in connection with anaesthesia and surgery. Nevertheless the work of Heptinstall and Joekes (1960) suggests that severe amyloidosis may cause only very slight renal dysfunction.

In Case 3, the development of fulminating Clostridial infection was the immediate cause of death. Although there is reason to suppose that the reticulo-endothelial system in rheumatoid arthritis may be hyperplastic or hyperactive (Roy, Alexander and Duthie, 1955) little direct evidence is available about the resistance of these patients to infection. Kellgren et al. (1958), have shown that undetected staphylococcal joint infection may be superimposed on rheumatoid arthritis in an appreciable proportion of cases. Mycotic infection, too, is an increasingly common complication of local steroid therapy. To what extent the progression of these infections is due to diminished capacity to resist bacterial or fungal invasion is not known. Nevertheless, it may be suggested reasonably that lowered resistance was a factor contributing to death in Case 3, and the possibility of infection should be borne in mind during the surgical care of patients with rheumatoid arthritis.

Finally, in Case 5, an example is described of unexpected and unexplained postoperative death in a patient with clinically mild rheumatoid arthritis. The clinical evidence suggested that respiratory obstruction was responsible, and although the larynx was not examined, pulmonary collapse with cerebral oedema supported this clinical diagnosis. This case emphasizes the necessity for close and prolonged postoperative supervision in cases of rheumatoid arthritis even in instances where the degree of disability is slight and the arthritis clinically inactive. The degree of clinical activity may be unrelated to the state or distribution of the pathological lesions.

SUMMARY

In five patients with rheumatoid disease respiratory difficulty during anaesthesia or unexpected postoperative death occurred.

It is emphasized that such patients may be difficult subjects for the induction of anaesthesia on account of arthritis and ankylosis of the small joints of the larynx, of the cervical spine and of the temporomandibular joints. In the same way the maintenance of adequate respiratory excursions during anaesthesia may be impeded by ankylosis of the costovertebral joints. Because of these manifestations of rheumatoid disease grave respiratory complications may be precipitated in the postoperative period. Following operation, the occurrence of interstitial pneumonia in rheumatoid arthritis may delay recovery. Particularly careful and continuous observation of these patients is necessary.

In other cases with rheumatoid arthritis apparently straightforward operative procedures are followed by unexpected death. The high inci-

dence of severe amyloidosis may determine a poor response to anaesthetic and analgesic drugs and in part account for these fatalities. Further, it is becoming increasingly evident that unsuspected and potentially dangerous infection may remain latent in joints which are the sites of rheumatoid arthritis. There is reason to suppose that such patients have an altered response to infections to which, in spite of their characteristically hyperplastic reticulo-endothelial systems, they exhibit abnormally low resistance.

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BLOOD OXYGEN SATURATION DURING ANAESTHESIA WITH VOLATILE AGENTS VAPORIZED IN ROOM AIR*

BY

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ANAESTHETISTS have long been in the habit of administering oxygen-rich gas mixtures. Some administer almost pure oxygen (Johnstone, 1959) and when pulmonary ventilation is allowed to become grossly deficient this is undoubtedly necessary if anoxia is to be avoided. Others take the view that an adequate minute volume should be ensured, and that it is therefore unnecessary to administer more than 20 per cent oxygen (for example, ordinary room air) except in occasional circumstances.

In Oxford this latter view is held (Parkhouse and Simpson, 1959) and a clinical trial has been concluded recently, in which 1,250 cases were anaesthetized with volatile agents vaporized in room air. Although this method of anaesthesia is quite satisfactory from the clinical point of view the writers are aware that there is doubt in some anaesthetists' minds as to whether the patient's colour is always a reliable guide to the adequacy of his arterial oxygen saturation. Accordingly it was decided to make a full investigation of blood oxygen levels during anaesthesia with volatile agents vaporized in room air.

PREVIOUS INVESTIGATIONS

Faulconer and Latterell (1949) studied arterial oxygen saturation during open drop ether anaesthesia. They recorded saturations as low as 70 per cent, but with open drop administration there is little control over the ether concentration and rebreathing may occur. More recently blood oxygen levels were measured during quantitative ether-air administration, using an E.M.O. inhaler (Ikezono, Harmel and King, 1959). The results of this investigation were on the whole favourable although only intermittent measurements were made (by direct arterial sampling) and thus transient falls in oxygen saturation could easily have been missed. Furthermore, one of the most satisfactory present-day applications of ether-air anaesthesia—its combination with muscle relaxants and controlled ventilation—was reported in only 9 cases. Nandrup (1959) reported on the use of low concentrations of ether in air with controlled ventilation. He found arterial oxygen saturation to be above or equal to normal on all occasions. Poppelbaum (1960) described oximetry during ether-air and halothane-air anaesthesia for thoracic operations. He recorded changes in saturation rather than absolute values, since his oximeter was preset to an arbitrary figure, but his measurements were continuous and the evidence suggested no difficulty in maintaining adequate oxygenation in the great majority of cases.

METHOD

In a series of 105 unselected patients, arterial oxygen saturations were measured before and during surgery and, in some cases, after return to the ward. Patients were anaesthetized with the E.M.O. inhaler and the Oxford Inflating Bellows. All patients were intubated with cuffed endotracheal tubes and respiratory minute volumes were measured from the expiratory side of a non-return valve. Ventilation during surgery was spontaneous or controlled, depending upon the circumstances. The volatile agents used, in separately calibrated inhalers, were ether, trichloroethylene, halothane and the azeotropic halothane-ether mixture.

Blood oxygen saturations were measured with the "Atlas Double Oximeter". This is a double oximeter which is unique in permitting simul-

*This work was carried out during the year in which one of the authors (P.V.C.) held the post of Surgical Research Assistant under the Nuffield Committee for the Advancement of Medicine, University of Oxford.

taneous ear and cuvette oximeter readings, samples for the latter being obtained by arterial puncture. The apparatus was thoroughly tested by comparison with the Van Slyke manometric method (Peters and Van Slyke, 1932) and its performance proved satisfactory: details will be published separately.

Well before the anaesthetic was due to begin a rubefacient was applied to the patient's ear and the ear unit of the oximeter was attached. The patient was then given pure oxygen to breathe and the oximeter dial was set to 100 per cent. The apparatus having been calibrated in this way, the patient was allowed to lie quietly, breathing room air, until the oximeter reading had fallen to a steady level: the resting arterial oxygen saturation was thus recorded. During operation, earpiece readings were checked against occasional arterial samples and if the discrepancy was greater than 3 per cent oximetry was abandoned. On the whole, agreement was surprisingly good although some shortcomings of the ear unit soon became apparent. For example, earpiece readings tended to fall during manipulation of the viscera or sudden haemorrhage, no doubt as a result of vasoconstriction and reduced blood flow through the ear (fig. 3). Also, in the steep Trendelenburg position venous congestion of the head and neck was responsible for some artificially low readings.

Resting Saturation

Although the normal resting arterial oxygen saturation is customarily taken as 95 per cent, a review of the literature reveals some confusion. Roughton, Darling and Root (1944) quoted the figure of 95.2 per cent—the mean of three previous observations. They then suggested that the figure should in fact be nearer 97 per cent, the discrepancy being due to errors in the estimation of the oxygen capacity of blood. Drabkin and Schmidt (1945), using a spectrophotometric method, proposed the even higher figure of 98.6 per cent. However, a more recent study using a gasometric technique (Lambertsen et al., 1952) found that for healthy nonsmokers the figure should be 97 per cent but that it may be as low as 93.6 per cent for smokers. Comroe and Walker (1948), from the results of oximetry, suggested a figure of 96.2 per cent for "ambulatory patients".

In the present series, resting arterial oxygen saturations were measured in the anaesthetic room in 96 patients, lying supine and quiet, after premedication. No account was taken of whether or not these patients were smokers, and not all of them were in good health. The mean figure obtained was 94.5 per cent with a standard deviation of 1.4, all saturations lying between 91 and 97 per cent.

RESULTS DURING AND AFTER ANAESTHESIA

Intubation and Extubation

Ten patients showed some degree of desaturation during intubation, the maximum fall being to 76 per cent; at this level a tinge of cyanosis was noticeable. Nine of these 10 patients were intubated after inflation with air alone and in the remaining case the anaesthetist gave only three breaths of oxygen. Weitzner, King and Ikezono (1959) have shown that, if intubation proves difficult and time-consuming, the apnoeic patient will not maintain full arterial saturation unless pre-oxygenation has been carried out. Present experience with the oximeter suggests that inflation of the lungs for 30 seconds with an oxygen-rich mixture ensures adequate arterial oxygen saturation for at least 1 minute during intubation.

Desaturation at the time of extubation was recorded in 17 patients. It was most commonly associated with the restoration of spontaneous breathing after use of the muscle relaxants, and with coughing and straining during tracheobronchial suction and removal of the endotracheal tube. Brief periods of anoxia may occur at this time with any form of general anaesthesia: figure 1 shows a comparison between a halothane-air anaesthetic and a "conventional" nitrous oxide-oxygen anaesthetic. In each case the endotracheal tube was removed without the previous administration of oxygen and in each case the patient's arterial oxygen saturation fell to the region of 30 per cent. It is the writers' common practice to administer an oxygen-rich mixture for some minutes prior to extubation and by this means severe desaturation may be prevented.

During Surgery

The cases may be grouped according to whether respiration was spontaneous or con-

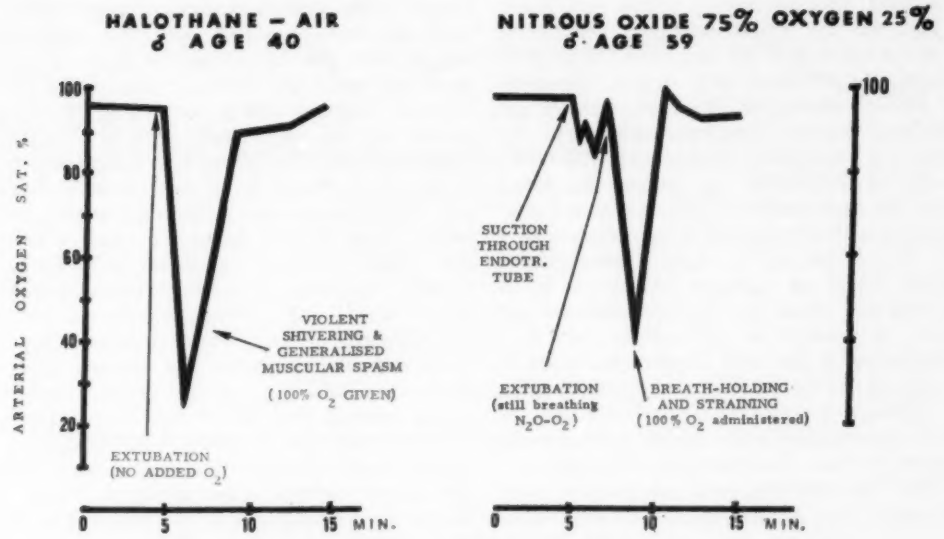

FIG. 1

Effect of extubation without pre-oxygenation on arterial oxygen saturation (see text).

trolled. The mean arterial oxygen saturation during operation may then be compared with the patient's resting level and thus desaturation can be appraised.

Controlled ventilation.

Table I shows the means of oximeter readings taken at 5-minute intervals throughout surgery in the 62 cases in which ventilation was controlled during anaesthesia. These means are expressed in terms of their difference from the patient's resting saturation level. The range of minute volumes in these 62 cases is also indicated. It may be seen from table I that arterial oxygen saturation remained within 2 per cent of the resting value in 57 of the 62 cases (92.0 per cent). The 5 cases in which mean arterial saturation was more than 2 per cent below the resting figure deserve some further consideration. Two of these patients had moderately severe cardiovascular disease, one having previously been in congestive failure. One case was an intrathoracic operation (see below). One was an exceptionally large, obese man whose average minute volume, 8 l., was almost certainly inadequate. The remaining case was a 60-year-old man

TABLE I

Arterial oxygen saturation and minute volume during controlled ventilation.

Mean arterial oxygen saturation during surgery	No. of cases	% of total	Minute volume during surgery (l.)	No. of cases	% of total
Above resting saturation	9	15	Above 12	1	2
Same as resting saturation	26	42	12–	3	5
1% below resting saturation	20	32	11–	3	5
2% " " "	2	3	10–	11	18
3% " " "	3	5	9–	17	27
4% " " "	2	3	8–	17	27
			7–	7	11
			6–5	3	5
Total	62	100		62	100

undergoing hemicolectomy; despite ventilation at 11 l./min his arterial saturation persistently fell to the region of 88 per cent unless the inspired mixture was enriched with oxygen. However, this patient's resting saturation was only 91 per cent, which suggests that some unsuspected respiratory or circulatory disease may have been present. In one further case oxygen was added during the anaesthetic in order to maintain arterial saturation within 2 per cent of the resting value: this was a patient in steep Trendelenburg position whose ear oximeter reading fell to 85 per cent and whose face appeared suffused and bluish. A brachial arterial sample showed a saturation of 91 per cent. Oxygen was added to the contents of the O.I.B. at the rate of 2 l./min, but although the arterial oxygen saturation, by direct measurement, rose to 98 per cent the appearance of the face remained unchanged.

When anaesthetizing poor risk patients, some reassurance may be derived from the addition of oxygen to the inspired mixture, although clinical judgment and experience with the oximeter suggest that this by no means always brings about any real improvement. Apart from the 6 cases discussed above, there were 9 other patients in this series whose general condition might well have been expected to make adequate oxygenation difficult. In all these 9 cases, however, average saturations during surgery remained within 2 per cent of the resting value without the addition of oxygen to the inspired mixture. Figure 2 illustrates an uncomplicated azeotrope-air anaesthetic with controlled ventilation.

Intrathoracic surgery was performed in 5 cases and table II shows that average saturations remained close to the patients' resting values without the use of additional oxygen, except in one case in which a fall of approximately 4 per cent occurred. However, this patient was almost certainly underventilated. Figure 3 illustrates oesophagogastrectomy under ether-air

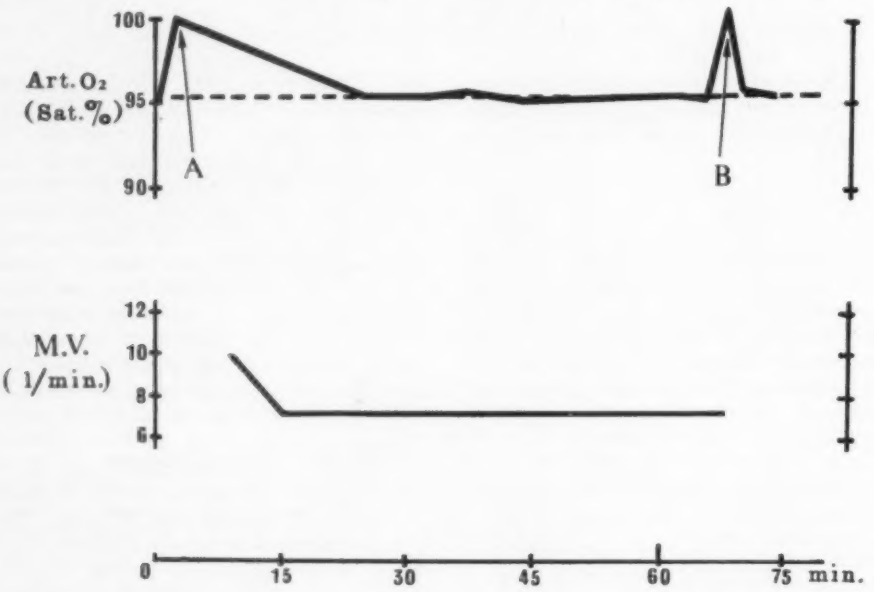

FIG. 2

Female, aged 40. Cholecystectomy. Azeotrope-air anaesthesia with gallamine and controlled ventilation. Dotted line on arterial oxygen saturation scale indicates patient's resting level.
A. Intubation after inflation with oxygen (note slow fall to normal saturation when the patient is being efficiently ventilated after pre-oxygenation).
B. Extubation after addition of oxygen.

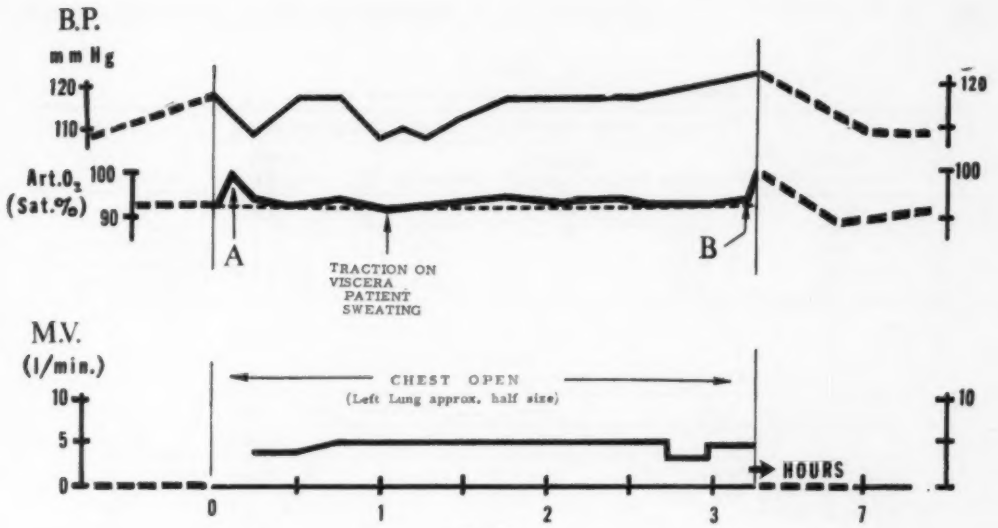

FIG. 3

Male, aged 75. Oesophagogastrectomy. Ether-air anaesthesia with d-tubocurarine and controlled ventilation. Vertical lines indicate duration of anaesthesia. Dotted line on arterial oxygen saturation scale indicates patient's pre-operative resting level.
A: Intubation after inflation with oxygen. B: Extubation after addition of oxygen.

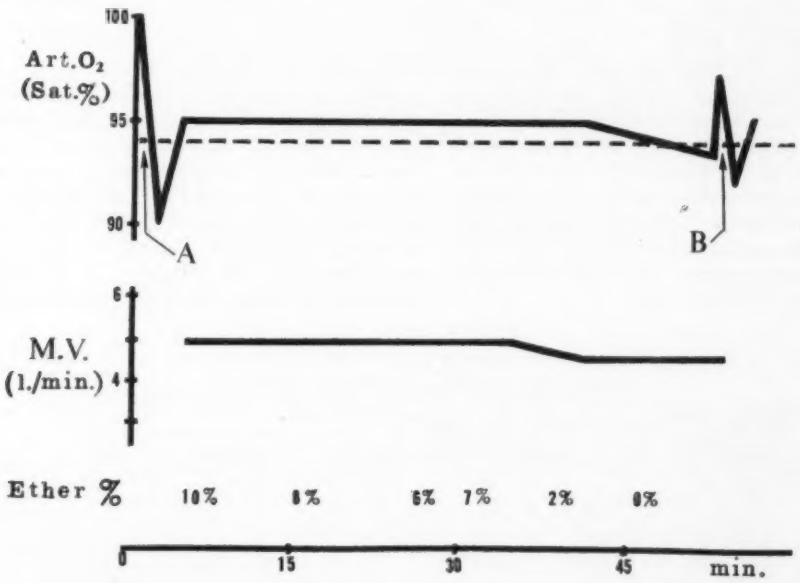

FIG. 4

Female, aged 78. Pinning of femur. Ether-air anaesthesia with intubation and spontaneous respiration. Dotted line indicates patient's resting arterial oxygen saturation.
A. Intubation after inflation with oxygen.
B. Extubation after addition of oxygen to inspired mixture.

TABLE II
Arterial oxygen saturation during thoracic surgery.

Case No.	Resting saturation (%)	Average during operation		Lowest during operation		Comment
		Saturation (%)	Minute volume (l.)	Saturation (%)	Minute volume (l.)	
1	93.5	92.5	10	91.0	10	——
2	94.0	94.0	10	92.5	9	——
3	95.5	94.0	11	92.0	10	Retraction of lung
4	93.0	91.0	9	85.0	8	Kinking of bronchus
5	95.0	91.0	8	89.0	6	Hypoventilation

TABLE III
Arterial oxygen saturation during spontaneous respiration.

Average saturation during surgery	Anaesthetic agent				
	Ether	Trichloroethylene	Azeotrope	Halothane	Total
Above resting saturation	2	1	–	–	3
Equal to resting saturation	7	–	–	–	7
1% below resting	8	1	1	–	10
2% " "	6	1	3	2	12
3% " "	0	1	2	2	5
4% " "	–	–	–	–	0
5% " "	1	–	1	–	2
6% " "	–	–	–	2	2
6+% " "	1	–	–	1	2
Total	25	4	7	7	43

anaesthesia in a 75-year-old man. Throughout more than 2 hours during which the left hemithorax was widely opened and the lung retracted out of the surgeon's way, arterial oxygen saturation remained at the pre-operative level (93 per cent). Immediately before closure of the thorax (and before reinflation of the left lung) a direct arterial sample was taken from the aorta as a check on the earpiece readings: the oxygen saturation of this sample was 92 per cent.

Spontaneous ventilation.

Forty-three patients breathed spontaneously during surgery, an illustrative case being shown in figure 4. Table III shows the means of 5-minute oxygen saturation readings during spontaneous breathing and it may be seen at once that there is a much greater range of values than during controlled ventilation (table I). This is not surprising, since the adequacy of spontaneous ventilation is largely dependent on the pharma-

TABLE IV
Minute volume during spontaneous respiration

Average minute volume during surgery (l.)	Anaesthetic agent				
	Ether	Trichloroethylene	Azeotrope	Halothane	Total
10+	2	1	–	–	3
9–10	3	–	–	–	3
8–9	3	1	–	–	4
7–8	7	1	1	–	9
6–7	5	1	2	1	9
5–6	4	–	2	2	8
4–5	1	–	2	2	5
3–4	–	–	–	2	2
Total	25	4	7	7	43

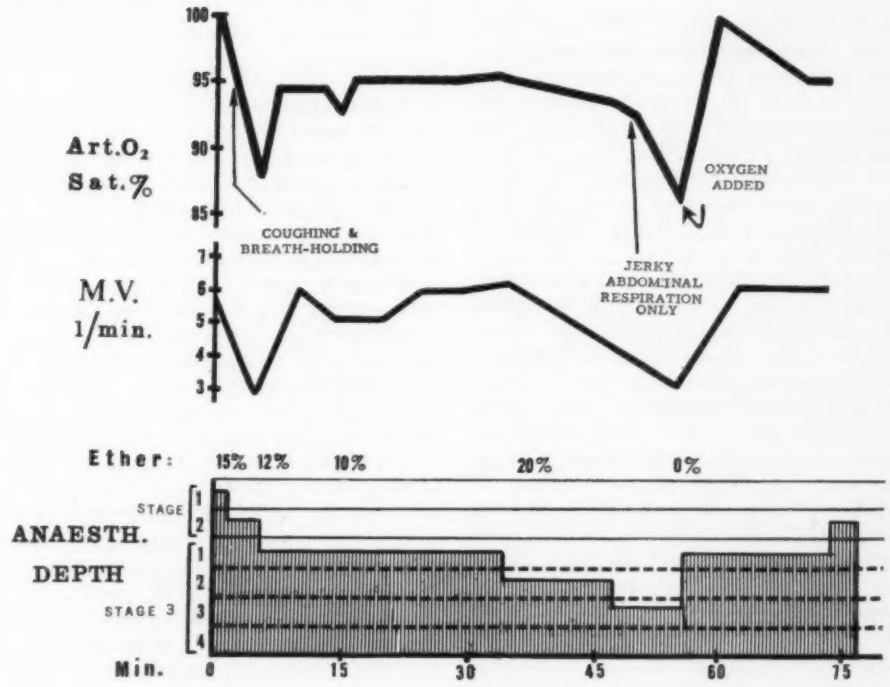

FIG. 5

Male, aged 10. Exploration of urethral stricture. Ether-air anaesthesia with spontaneous respiration. Note sudden fall in arterial oxygen saturation during third plane anaesthesia: oxygen was added before cyanosis became apparent.

TABLE V

Arterial oxygen saturation during the postoperative period

Pre-operative resting saturation (%)	Average saturation during operation (%)	During postoperative period		Difference (pre-operative minus postoperative) (% saturation)
		Time after operation (hr)	Saturation (%)	
94.0	92.5	1	89.0	5.0
96.5	96.0	1	94.0	2.5
94.5	94.0	1	92.0	2.5
96.0	94.5	3	93.0	3.0
93.0	94.0	6	91.5	1.5
91.0	91.5	4	85.0	6.0
92.5	92.0	3	90.5	2.0
95.0	95.5	7	94.0	1.0
97.0	96.0	4	93.5	3.5

cological properties of the anaesthetic drug used. Minute volumes during spontaneous respiration are given in table IV.

Although arterial oxygen saturations were generally satisfactory during spontaneous respiration with ether and trichloroethylene, they were less so with the azeotropic mixture, and decidedly unsatisfactory with halothane. This accords with the clinical finding that when halothane is used without a muscle relaxant cyanosis is common unless respiration is assisted, or an oxygen-rich mixture administered. Altogether in the present series it was necessary to add oxygen or assist ventilation in 4 cases, and in 3 of these halothane was the agent used. It should be noted, however, that during anaesthesia a minute volume lower than expected does not necessarily imply deficient oxygenation; we have recorded satisfactory arterial saturations with minute volumes as low as 4 l., and a similar finding has recently been reported from America (Ikezono, Harmel and King, 1959).

In 3 cases (2 ether and 1 trichloroethylene) the patient's respiratory minute volume was raised during light anaesthesia, and the mean arterial oxygen saturation was above the resting figure. It is interesting to compare the mean figures for minute volume in the controlled respiration and spontaneous respiration groups: in the controlled respiration group the mean was approximately 9 l./min and in the spontaneous respiration group approximately 6 l./min. The effect of different anaesthetic agents is well illustrated in the spontaneous respiration group, respiratory depression being greatest with halothane (table IV).

Transient falls in arterial oxygen saturation were observed in spontaneously breathing patients, associated with coughing or breath holding. Saturation quickly returned to a satisfactory level when regular breathing was resumed. Such incidents of transient anoxia are, of course, liable to be associated with any technique if a spontaneously breathing patient is allowed to become unduly lightly anaesthetized.

In practically all patients in the present series anaesthesia was maintained at a light level, with or without the use of muscle relaxants. In one case, however, an opportunity arose for measuring arterial oxygen saturation during deep ether anaesthesia (fig. 5). Although the patient's minute volume declined progressively with deepening anaesthesia, his arterial oxygen saturation fell quite suddenly.

The Postoperative Period

In 9 cases arterial oxygen saturation was measured after the patient's return to the ward: the results are shown in table V. These measurements were confined to patients who had undergone thoracic or upper abdominal operations and who would therefore be expected to have considerable pain and limitation of respiratory movement in the early postoperative period. Most of them had received some postoperative sedation; none of them was a particularly poor risk and none was causing anxiety to the medical or nursing staff at the time measurements were made. This is a small group of cases but it serves to illustrate the point that in no single instance was the postoperative arterial oxygen saturation as high as the saturation recorded during anaesthesia with a volatile agent and room air. On several occasions it was appreciably lower.

DISCUSSION

Man has evolved to breath air; we know from our common experience, and from the management of respiratory failure, that as long as our lungs are replenished, either spontaneously or artificially, with a sufficient quantity of air no serious harm will result. Common sense therefore suggests that for the resting, anaesthetized patient, air should be a satisfactory vehicle for volatile drugs and that this should hold true whether respiration be spontaneous or controlled so long as it be free and undepressed. This contention is supported by the present study. Even when a patient's respiratory or cardiovascular system is abnormal, supplementary oxygen is not always essential or even beneficial, although it can so easily be added to the inspired mixture that there seems no point in withholding it from sheer bravado.

During spontaneous ventilation some degree of arterial desaturation may occur as a consequence of either respiratory obstruction or respiratory depression. When ether is employed serious falls in arterial oxygen saturation do not occur except in the deepest planes of anaesthesia,

which are nowadays better avoided by the use of muscle relaxants. The danger of respiratory depression from other causes, for example heavy premedication or thiopentone overdosage must, of course, be borne in mind. When respiration must, or may, be interrupted, as during intubation and extubation, the anticipatory addition of oxygen is to be recommended.

It is easy for the anaesthetist to lay undue emphasis on 100 per cent arterial oxygen saturation throughout surgery, without giving sufficient thought to the patient's normal saturation level and, more particularly, to the probable state of affairs in the early postoperative period. After return to the ward, the great majority of patients are left to breathe air, without any additional oxygen, at a time when they may have considerable respiratory embarrassment. Arterial oxygen saturation is often lower at this time than during the administration of a volatile anaesthetic agent in air.

SUMMARY AND CONCLUSIONS

An "Atlas Oximeter" was used to measure arterial oxygen saturation in 105 patients anaesthetized by means of volatile agents vaporized in room air. Measurements were made pre-operatively, during surgery, and sometimes in the post-operative period. During controlled ventilation, providing oxygen was administered prior to intubation and extubation, arterial oxygen saturations compared favourably with the normal for the patient. During spontaneous ventilation, arterial oxygen saturation remained satisfactory in the great majority of cases unless marked respiratory depression occurred. When respiratory depressants such as halothane are used the anaesthetist should be prepared to assist the respiration or use additional oxygen. Arterial oxygen saturations measured during the early postoperative period were lower than those recorded during surgery.

ACKNOWLEDGMENTS

We should like to express our thanks to Professor Macintosh and Dr. H. G. Epstein for help and encouragement with this work, and to the anaesthetists of the United Oxford Hospitals for permission to make measurements on patients anaesthetized by them.

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RUBBER DERMATITIS: AN ANAESTHETIC PROBLEM

BY

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RUBBER dermatitis is a well recognized disease (Leider, Furman and Fisher, 1952). It occurs both with the natural and synthetic product (Schwartz, 1945). The substance responsible, however, is rarely the rubber itself but is usually one or more of the organic chemicals used in the conversion of the raw material into the finished product, especially accelerators and antioxidants (Bonnevie and Marcussen, 1944; Petro, 1942). Accelerators such as mercaptobenzothiazole (MBT) C_6H_4NS (CSH) speed up vulcanization—the combination of rubber with sulphur to confer strength and elasticity—from hours to minutes. MBT is present in rubber in a concentration of up to 3 per cent (Gaul, 1957) and is commonly the cause of rubber dermatitis (Wilson, 1960; Bonnevie and Marcussen, 1944).

If rubber containing MBT is left in distilled water overnight this will acquire a characteristic bitter taste as some of the MBT passes into solution. Because of this bitter taste MBT is not used in rubber manufactured for the food industry (Muller, 1960).

Begenau (1951) reported the case of a patient, sensitive to rubber, in whom an attack of dermatitis was precipitated by an anaesthetic mask. The sensitizing agent was not identified. The case here reported is similar, but in it elimination of contact with MBT prevented the appearance of symptoms after anaesthesia almost completely.

CASE REPORT

A general practitioner, aged 61, suffering from aortic stenosis, was admitted to the Brompton Hospital for transventricular aortic valvotomy. In 1942 he had suffered severe rubber dermatitis from contact with the facepiece of an R.A.F. respirator. (This condition was a service problem at the time (Petro, 1942).) He was then investigated by Dr. F. Ray Bettley (1952) and found to be exquisitely sensitive to MBT, even at a dilution of 1 part in 100,000,000,000,000. Indirect contact through two other persons or articles could precipitate an attack. He described the eruption as "like impetigo".

Desensitization was not attempted because of the risk and unlikelihood of success. Although antihistamines lessened the severity of his attacks, they did not prevent them. He had not tried cortisone, but, in any case, this does not appear to have much prophylactic effect (Sulzberger, Witten and Zimmerman, 1952). By taking extreme precautions, such as completely eliminating rubber from his household and wearing cotton gloves, he had greatly reduced the incidence and severity of attacks and had not had one for several months before admission.

It was obviously essential to take the greatest care to avoid precipitating an attack whilst in hospital. Extensive enquiries were therefore made concerning the MBT content of the rubber used in the manufacture of the various pieces of equipment likely to be used in this case (table I). (The list is incomplete, as several manufacturers gave information in confidence, and for various reasons do not wish their names to be published.) However, it would be wrong to assume that articles similar to those listed are invariably free from MBT, whatever their source.

Most red rubber surgical and anaesthetic equipment and some antistatic rubber, such as corrugated tubing, pressure tubing, and operating table mattresses, contain MBT, depending on the manufacturer. Apart from the above articles therefore, it was decided to use plastics as follows:

"Portex" or "Polythene" substituted for rubber: anaesthetic gas tubing; endotracheal catheter mount (a Cobb's T-piece was used); airway; "Neoplex" suction catheter (Endoscopic Instrument Co. Ltd., Sherland Road, London, W.9); brachial stethoscope tubing; operating macintoshes; vessel snares; drainage tubes.

Because of the routine use of diathermy in this hospital, explosive anaesthetic agents are not used. The need for conducting rubber to avoid sparks

TABLE I

Articles not containing MBT.

"Everseal" antistatic face-masks. (Medical and Industrial Equipment Ltd., New Cavendish Street, London, W.1.)
Antistatic rebreathing bags. (Charles King Ltd., 27 Devonshire Street, London, W.1.)
Latex armoured endotracheal tubes and cuffs. (Charles King Ltd.)
None of the latex products of the company manufacturing these articles contains MBT. For the operation a "Portex" endotracheal tube (Medical and Industrial Equipment Ltd.) with a latex cuff was used.
Latex surgeons' gloves. (Veedip Ltd., St. Helens Works, Slough, Bucks.)
Latex tubing on the C/H disposable recipient set. (Capon Heaton & Co., Ltd., Stirchley, Birmingham, 30.)
Red and black rubber discs in transfusion bottle caps. (R. B. Turner, & Co., Finchley, London, N.3.)
"Elastoplast" adhesive bandage. (Smith & Nephew Ltd., Welwyn Garden City, Herts.)

due to static electricity could therefore safely be ignored.

The following articles were covered in plastic bags or tubing: operating-table mattress and cushions; macintosh covered arm-board; sphygmomanometer; Higginson's syringe (for pressure transfusion).

Fortunately the diathermy handles were of wood, as the patient described vulcanite as "a terror!" A pin-index Boyle's machine (British Oxygen Co. Ltd.) was used, together with a Waters canister.

Anaesthesia was uneventful and the operation was performed at normal temperature. Antihistamines were not used.

Apart from a transient itching of his face where the elastic of a plastic oxygen mask had touched him, his dermatitis gave no trouble. It has not been possible to find out the composition of this rubber.* Once awake, he took his usual precautions against exposure to rubber and made a satisfactory recovery from the operation.

COMMENT

Apart from the risk of producing an attack of dermatitis, there were two other possible dangers in this case. Although sensitization dermatitis does not necessarily involve the mucous membranes (Bettley, 1960), this patient once had an eruption in his mouth after eating a sweet which had been in contact with rubber, and there was therefore a risk of laryngeal oedema in using an endotracheal tube containing MBT. Cardiovascular collapse following the use of nickel intravenous equipment in patients sensitive to nickel has been reported (Stoddart, 1960) and in this patient a similar reaction might have occurred with MBT in the transfusion set in view of his exquisite sensitivity to this substance.

*Since this article was written the manufacturers have confirmed the presence of MBT in the elastic of these masks.

SUMMARY

An account is given of a patient with dermatitis due to mercaptobenzothiazole (MBT), an accelerator used in the manufacture of rubber. The precautions taken to avoid exposing him to this substance in the operating theatre are described.

ACKNOWLEDGMENTS

I wish to thank Mr. O. S. Tubbs and Dr. Ruth Mansfield for permission to publish details of this case. I am grateful to the various manufacturers and the firms they supply for a generous supply of information.

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CORRESPONDENCE

PROLONGED APNOEA AFTER SUXAMETHONIUM INCREASED INTRACRANIAL PRESSURE

Sir,—Many cases of prolonged apnoea after suxamethonium injection have been reported in the literature. We have had a case the cause of which was rather unusual.

CASE REPORT

A boy of 12 years, height 152 cm, weight 34 kg, was admitted for ventriculography and arteriography followed by explorative craniotomy under general anaesthesia; these were all performed on the same day. The patient was admitted to the hospital complaining of frontal headache, morning sickness, loss of appetite and weight, tiredness, intermittent pyrexia, diplopia and paraesthesia in both hands—which happened covering a period of 6 months, and are described in sequence. Throughout the illness, the mental state remained normal with no history of loss of consciousness, convulsions or paralysis.

Ophthalmoscopy revealed normal sight and field of vision. The disc showed papilloedema with decreased venous dilatation. On the right side there were small lateral haemorrhages with marked retinal oedema. There was apparent weakness of left abducens nerve. Vestibular investigation did not reveal any abnormality, the e.e.g. showing slightly abnormal waves but no side prominence or abnormal focus.

Management of anaesthesia. After premedication with atropine 0.5 mg, anaesthesia was induced with 150 mg + 50 mg thiopentone 2.5 per cent followed by suxamethonium 50 mg intravenously. There was marked muscle twitching after this injection. The larynx and trachea were sprayed with 4 per cent cocaine solution. While this was being done the patient moved his legs and seemed to be wakening up. Two further doses of thiopentone 100 mg were given. Endotracheal intubation was performed without difficulty and the patient was ventilated with a mixture of 50 per cent nitrous oxide and oxygen at a flow of 4 l./min in a semiclosed system. Auscultation revealed equal air entry into both lungs. During induction the blood pressure fell to 80 mm Hg systolic from 110 mm Hg and then rose to 90 mm Hg; the pulse rate was 120 to 130 per minute. There was no return of spontaneous respiration. After 30 minutes the apnoea still persisted, therefore ventricular puncture was decided upon. Cannulae were introduced through boreholes into both posterior horns which revealed the cerebrospinal fluid pressure to be 350 to 400 mm H_2O. About 20 ml of cerebrospinal fluid was removed and immediately spontaneous respiration with normal rate and rhythm returned and continued.

Ventriculography showed dilatation of the ventricular system. Vertebral arteriography was suggestive of a space-occupying lesion in the right cerebellar hemisphere. A posterior fossa craniotomy revealed no tumour but a dilated foramen of Magendie, central in position. Both cerebellar hemispheres were normal in appearance and consistency and there was no other sign of tumour. From an area of meningeal irritation a biopsy was taken and the wound was closed.

The postoperative course was uneventful and ophthalmoscopy one week later showed persistence of two dioptres of papilloedema with blurring of the disc margins and moderate peripapillary oedema. Venous pulsation was present but reduced. No retinal haemorrhages were noted. The biopsy report from the meningeal specimen showed lymphocytic arachnoiditis.

The causes of prolonged apnoea for 35 minutes after induction of anaesthesia in this case may be:

(1) The dose of thiopentone of 400 mg in a patient whose bodyweight was 34 kg. This could have caused a repiratory depression of sufficient degree to result in cessation of respiration.

(2) A toxic effect from the 4 per cent cocaine solution used in local analgesia.

(3) Increased intracranial pressure.

The immediate resumption of spontaneous respiration following reduction in the cerebrospinal fluid pressure seems highly significant. It would appear therefore, in this case, that the cause of prolonged apnoea was the further increase in intracranial pressure produced by the suxamethonium injection (a recognized effect of this drug) and the mechanical displacement leading to a "coning" of the medulla into the foramen magnum.

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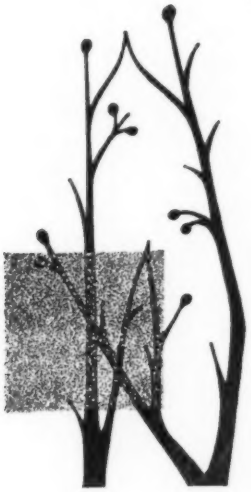

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